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Synthesis of N-Acyl α -Amino Amides and the Study of Chiral Acyclic Diaminocarbenes

by

Ntaganda, Rukundo

A Thesis

Submitted to the Faculty of Graduate Studies
through the Department of Chemistry and Biochemistry
in Partial Fulfillment of the Requirements for
the Degree of Master of Science at the
University of Windsor

Windsor, Ontario, Canada

2009

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Declaration of Co-Authorship

I hereby declare that this thesis incorporates material that is result of joint research under the supervision of Dr. Avinash Thadani, as follows:

- Tamara Milovic contributed to the synthesis and purification of α -keto esters (Ch. 1).
- Mira Beshai collaborated in the synthesis of the formamidine salts presented in Ch. 2.
- Dr. Jorge Tiburcio solved one crystal structure presented in Ch. 1 (**19a**).
- Ben Cooper, and Dr. Charles Macdonald solved crystal structures presented in both Chapter 1 (**19h** and **19k**), and Chapter 2 (**102-I** and **117**).

I am aware of the University of Windsor Senate Policy on Authorship and I certify that I have properly acknowledged the contribution of other researchers to my thesis.

I certify that, with the above qualification, this thesis, and the research to which it refers, is the product of my own work.

Declaration of Previous Publication

This thesis includes one original paper that has been previously published in peer reviewed journals, as follows:

Ch. 1: R. Ntaganda, T. Milovic, J. Tiburcio and N. Thadani Avinash, *Chem. Commun.*, **2008**, 4052-4054. (DOI: 10. 1039/b808302a)

I certify that the above material describes work completed during my registration as graduate student at the University of Windsor.

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Abstract

The first chapter of the thesis covers a simple one-step methodology to synthesize N-acyl- α -amino amides directly from α -keto esters and ammonia. The factors that govern this reaction have been studied, and the mechanism through which it proceeds has been briefly investigated. The substrate scope of the methodology was found to be broad, and a wide range of N-acyl α -amino amides were synthesized in good to excellent isolated yields. In all cases the desired products were isolated in high purity by crystallization, and did not require further chromatographic purification. The X-ray crystal structures of three N-acyl α -amino amides were also obtained. In addition, the acid hydrolysis of these derivatives was shown to furnish the corresponding unnatural α -amino acids in high yields after purification by ion exchange chromatography.

The second chapter of the thesis describes our progress towards the synthesis of chiral acyclic diaminocarbenes (ADC), and their ultimate application as ligands in enantioselective catalysis. Towards this end, we have synthesized six chiral formamidine salts, as precursors to chiral ADC with either C_2 - or C_1 -symmetry, in good to excellent yields. An X-ray crystal structure of a C_2 -symmetric formamidine iodide salt was obtained. In addition, the attempted formation of a chiral ADC-metal complex from the corresponding formamidine salt, via deprotonation with LDA and reaction with the metal salt, instead resulted in the isolation of the corresponding urea. The structure of the urea was proven by X-ray crystallography, and its formation was assumed to arise from the oxidation of the free chiral ADC with adventitious oxygen.

Acknowledgement

I acknowledge and deeply thank my supervisor Dr. Avinash Thadani, for allowing me to work on such interesting projects, for his invaluable advices and encouragements as well as his guidance throughout my studies. I thank everybody I have had a chance to work with: Guangshi Lu, Bharthesh Dhudshia, Mira Beshai, Ryan Mills, Eric Bushnell, Tamara Milovic, Jennifer Scott, and Christopher Mireault for their support and friendly attitude. In addition, I thank Tamara and Ryan for proofreading my final thesis.

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To my family and friends, your inspiration and support will always be appreciated.

Abbreviations:

ADC	Acyclic diaminocarbenes
Ar	Aryl substituents
B ⁻ /BH	Brønsted base/conjugate acid
BDE	Bond Dissociation energy
bpy	2,2'-bipyridine
br	Broad
Conv.	Conversion
Cy	Cyclohexyl
δ	Chemical shift in ppm (NMR)
d	Doublet
DIP-Cl	Chlorodiisopinocampheylborane
DMA	N,N-dimethylacetamide
E _a	Activation energy
ee	Enantiomeric excess
equiv	Equivalence(s)
Et	Ethyl
IR	Infrared
LDA	lithium diisopropylamide
m	Multiplet
M	metal
Met	Methyl
Ms	Methanesulfonyl
MsCl	Methanesulfonyl chloride
NHC(s)	N- Heterocyclic carbene(s)
NMR	Nuclear Magnetic Resonance

Ph	Phenyl
PhMe/ PhCh ₃	Toluene
Py	Pyridine
R	Alkyl group unless otherwise defined
s	Singlet
TEA	Triethylamine
TEP	Tolman Electronic Parameters
THF	Tetrahydrofuran
TOF	Turnover frequency
TON	Turnover number

Table of Contents

Declaration of Co-Authorship	ii
Declaration of Previous Publication	ii
Abstract	iv
Acknowledgement	v
Abbreviations:.....	vi
Chapter I: Synthesis of N-acyl-α-amino amides from α-keto esters and ammonia.....	1
1. Introduction	1
1.1. Introduction to nitrogen	1
1.2. Ammonia	2
1.3. Amino acids and their synthesis	2
1.3.1. Strecker method	3
1.3.2. Hydrogenation of unsaturated amino acids	4
Hydrogenation of α,β -dehydro- α -amino acid derivatives	4
Hydrogenation of α -imino acids and α -imino esters.....	4
1.4. Prior related work from our group	5
2. Results and Discussion.....	7
Optimization studies	9
Synthesis of α -keto esters from boronic acid reagents.....	11
Scope of application	11
Proposed mechanism and supporting studies.....	14
Conclusion	15
3. Experimental.....	15
3.1. α -keto esters	15
3.1.1. Synthesis.....	15
3.1.2. Characterization	16
3.2. N-acyl- α -amino amides	18
3.2.1. Synthesis.....	18
3.2.2. Characterization	18
Chapter II: Synthesis of chiral formamidine salts as precursors to acyclic diaminocarbenes.....	58
1. Introduction.....	58
1.1. Enantioselective catalysis	58
1.1.1. Catalysis	58
1.1.2. Organometallic complexes in catalysis	59
1.1.3. Multiplication of chirality	60
1.1.3.1. C_2 -symmetric ligands.....	61

1.1.3.2. C ₁ -symmetric ligands	63
1.2. Carbenes	64
1.2.1. Schrock carbenes and reactivities	65
1.2.2. Fischer carbenes and reactivities	66
1.2.3. Diaminocarbenes	66
1.2.3.1. N-heterocyclic carbenes (NHCs)	66
Historical breakthroughs	67
General synthesis of NHCs	69
Synthesis of azolium salts	70
Electronic and steric stabilization of NHCs	71
NHC-transition metal complexes and catalysts	72
Chiral monodentate NHCs in enantioselective catalysis	75
1.2.3.2. Acyclic diaminocarbenes	81
1.2.3.2.1. N,N,N',N'-tetrasubstituted aminomethyleneiminium salts	84
2. Discussion	87
3. Conclusion and future work	94
4. Experimental	94
General notes:	94
General procedure to synthesize formamidine salts	94
Counterion exchange with tetrafluoroborate	95
Counterion exchange with iodide	95
Characterization data	95
References:	111
Appendix I: Crystal structure tables for 19a	115
Appendix II: Crystal structure tables for 102	121
Appendix III: Crystal structure tables for 117	135
VITA AUCTORIS	142

Chapter I:

Synthesis of N-acyl- α -amino amides from α -keto esters and ammonia^{*†}

1. Introduction

1.1. Introduction to nitrogen

Molecular nitrogen is an abundant gas in nature, comprising about 78% of the atmospheric air.^{1, 2} It is a stable molecule due to the robust triple bond between the two nitrogen atoms. Molecular nitrogen only reacts with other elements under harsh conditions (elevated pressure and temperature) in presence of transition metal catalysts, and due to this reason, its synthetic uses are restricted. It should be noted, however, that Mother Nature has her own ways to build a whole host of nitrogen containing molecules through “nitrogen fixation”³ and other metabolic processes in plants and living organisms. The complexity and the diversity of these molecules present inspirational challenges to scientists in many research areas including synthesis, therapeutic applications, drug design, and material chemistry.⁴ For example, nitrogen is found in 90% of synthetic therapeutic compounds.⁵ It also has properties relevant in materials chemistry such as the ability: (i) to form polarized C-N bonds, (ii) to easily form ionic species, (iii) to hydrogen bond to other molecules and, (iv) to coordinate to metals through dative bonds.

Due to the aforementioned nitrogen properties, synthetic chemists⁶ require a wide variety of affordable N-containing building blocks that can be used to synthesize more

^{*} Tamara Milovic synthesized the required non-commercial α -keto esters.

[†] Dr. Jorge Tiburcio solved the crystal structure of **19a**, whereas Ben cooper and Dr. Macdonald solved the crystal structures of **19h** and **19k**.

functionalized compounds. Therefore, the development of new practical, cost effective and environmentally conscious synthetic methods to these compounds is of great importance.

1.2. Ammonia

Ammonia is one of the simplest molecules generated industrially from N_2 gas and H_2 gas through the Haber-Bosch process.¹ Alternative milder conditions to generate ammonia from N_2 and H_2 have also been reported.^{1, 7-10} Ammonia is among the cheapest commodity chemicals sold in bulk quantities, and it is used industrially to synthesize a wide variety of small molecular weight amines that includes diethyl amine, triethyl amine, caprolactam, and acrylonitrile. There is also an increasing interest to use ammonia as a primary feedstock in the synthesis of more functionalized amines.

Ammonia is a colorless alkaline gas at ambient conditions with a boiling point of $-33\text{ }^{\circ}\text{C}$ at 746 mm Hg. It reacts with acids to form the corresponding ammonium species. For example, it reacts with water to form ammonium hydroxide solution (NH_4OH), and with HCl it forms the corresponding ammonium chloride salts (NH_4Cl). For synthetic purposes, ammonia requires the use of high pressure vessels and reactors.

1.3. Amino acids and their synthesis

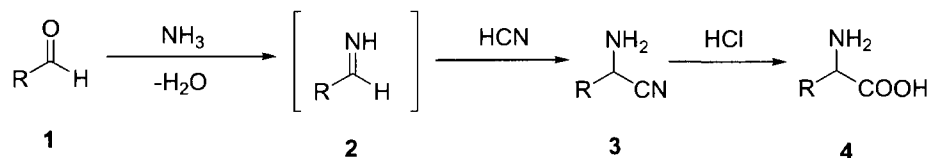
There are twenty natural amino acids, and these are building blocks of more complex biological macromolecules such as enzymes, protective and structural proteins. Natural α -amino acids share a distinctive structural feature: they all have a carboxyl group and amino group bonded to the same carbon. To this carbon, another functional group is bonded and the nature of this functional group distinguishes one amino acid from another, in terms of their physical and chemical properties.

In addition to these natural amino acids, biological and medicinal chemists require the use of unnatural amino acids with varied α -functional groups and also α,α -disubstituted amino acids.¹¹ The synthesis of these unnatural amino acids can be achieved through different ways that are briefly described next.

1.3.1. Strecker method

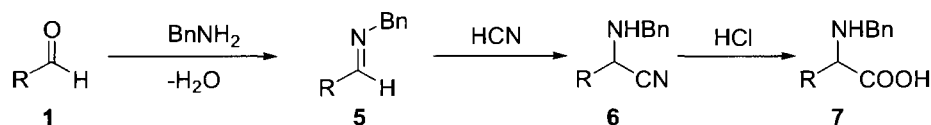
The classic method to synthesize amino acids is the Strecker method. Aldehydes or ketones react with ammonium salts to form the presumed unsubstituted imines **2** which are then reacted with cyanide to furnish the α -amino nitriles **3**. The hydrolysis of the nitrile group then affords the corresponding amino acids **4** (Equation 1). Aldehydes yield α -monosubstituted while ketones yield α,α -disubstituted amino acids. This method, which dates to the early 1850s, still finds use today. However, it has gone through a great deal of improvement such that enantioselective variants are also known.¹²

Equation 1



Ammonia can also be replaced by a secondary amine, and thus hydrogen cyanide is added to relatively more stable N-substituted imines **5** (Equation 2). The old process to impart enantioselectivities to this important reaction uses chiral primary amines in place of ammonia to form chiral imines. The nucleophilic addition of cyanide can then proceed in a diastereoselective manner. The work up consists of the nitrile hydrolysis and also the removal of the nitrogen substituent to get the enantioenriched amino acid.¹³⁻¹⁶

Equation 2



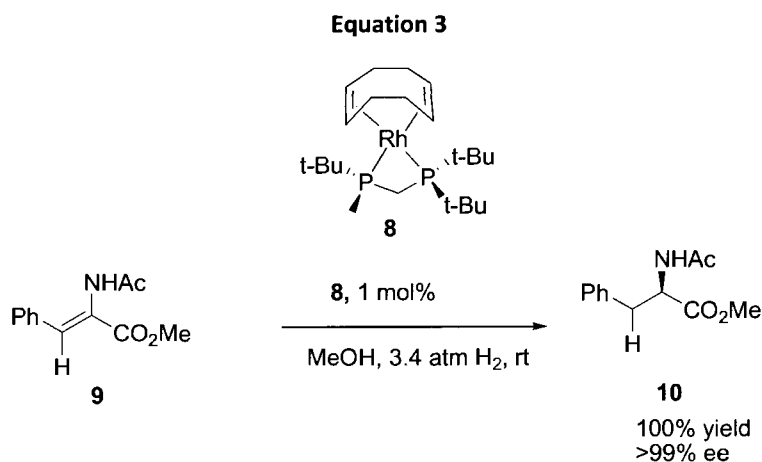
Imines, such as **5**, are known to be activated toward nucleophilic addition through interactions with H-bonding donors,¹⁷⁻²² Lewis acids,^{23, 24} and Brønsted acids.²⁵ With such chiral reagents considerable levels of enantioselectivity in the addition of cyanide have been

achieved.¹² The enantioselective cyanide addition to imines has also been achieved with chiral phase transfer catalysts.²⁶

1.3.2. Hydrogenation of unsaturated amino acids

Hydrogenation of α,β -dehydro- α -amino acid derivatives

The hydrogenation of α,β -dehydro- α -amino acid derivatives is one of the most commonly used reactions to synthesize aliphatic amino acids. A wide variety of transition metal catalysts can be used, including Ru, Ir,²⁷ Rh, Pd,²⁸ Co complexes.²⁹ However, the Rh catalysts are usually found to be the most suitable for the aforementioned transformation. With Rh complexes, relatively lower reaction pressures are required, and excellent enantioselectivities have been obtained (Equation 3).³⁰

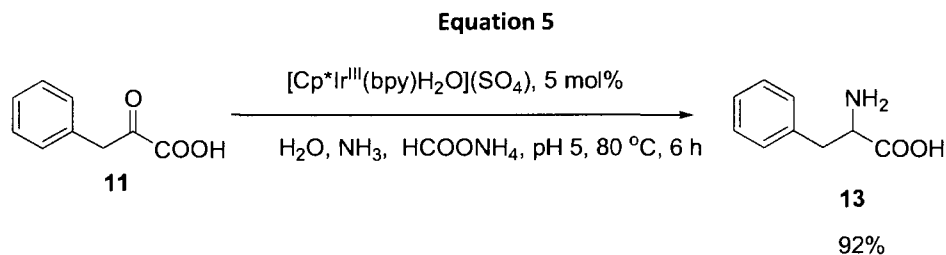
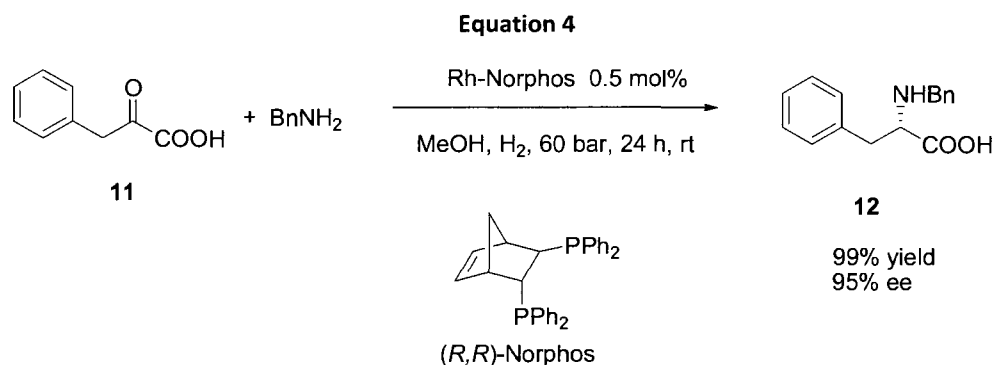


Hydrogenation of α -imino acids and α -imino esters

The hydrogenation of the α -imino esters and α -imino acids generated from the corresponding α -keto esters or α -keto acids has also been employed as another route to α -

amino acids. This method can be carried out with isolated imines or through one pot reductive amination (Equation 4).³¹

Ogo and coworkers have also shown that ammonia can be used in presence of an Ir catalyst to convert α -keto acids directly to the corresponding α -amino acids (Equation 5).³² For optimal chemoselectivity (i.e. to furnish α -amino acids over α -hydroxy carboxylic acids), the pH of the reaction mixture must be carefully controlled; the sensitivity varies from substrate to substrate. In addition, the hydride source should be compatible with the reaction conditions.



1.4. Prior related work from our group

Primary and secondary amines are known to react with aldehydes and ketones to give N-substituted imines that can react with a wide range of nucleophiles to give secondary and tertiary amines.^{33, 34} On the other hand, similar work with ammonia to afford the primary amine has been much less studied, despite the inherent cost reduction and environmental benefits that flow from the reduction of the generated chemical waste. In our group, the

When the reaction was run at elevated temperatures without the crotyl boronic acid reagents, the N-acyl- α -amino amide **19a** was instead obtained as white crystals (Equation 6).³⁶ The structure of the N-acyl- α -amino amide was confirmed by X-ray crystallography as shown in Figure 1.

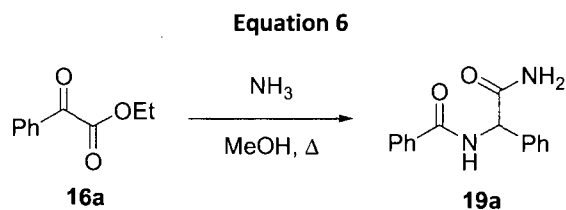
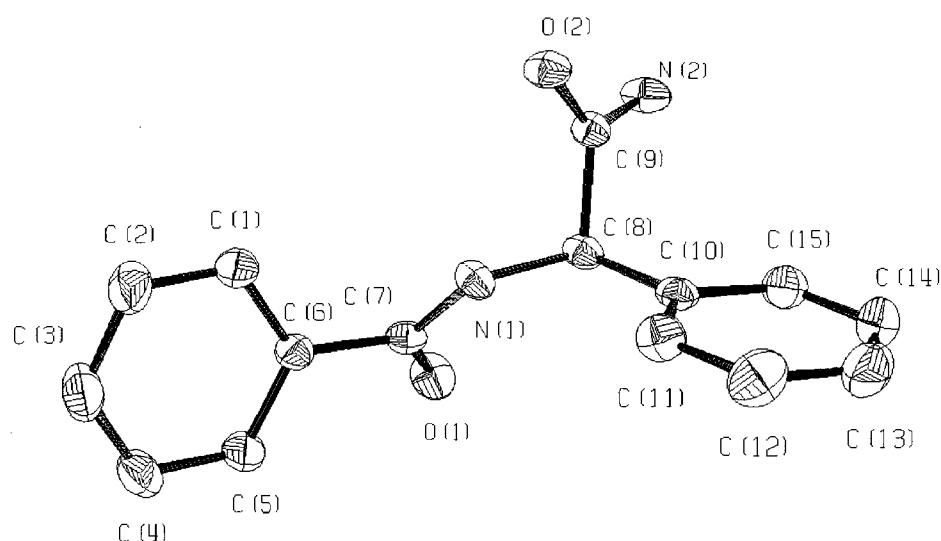


Figure 1: Ortep crystal structure of 19a, at 30% thermal ellipsoid probability, hydrogen atoms are omitted for clarity

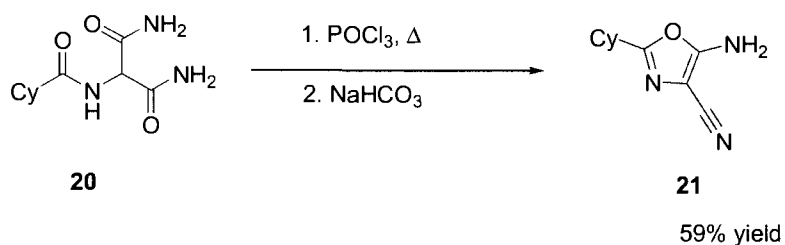


2. Results and Discussion

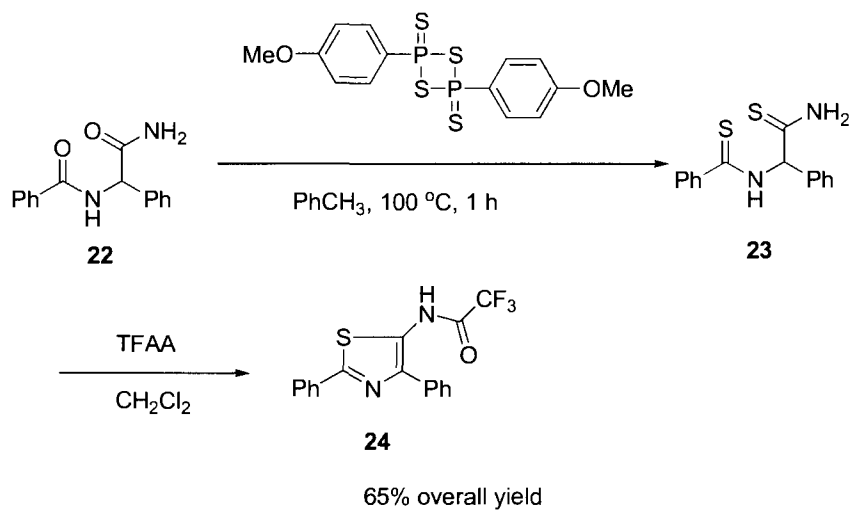
N-acyl- α -amino amides can be used to synthesize other useful compounds. For example, oxazoles **21** (Equation 7),³⁷ aminothiazoles **24** (Scheme 3),³⁸ can be easily synthesized from the corresponding N-acyl- α -amino amides. These heterocycles are known to exhibit therapeutic properties.^{37, 38} In addition we have also shown that the acid hydrolysis of the N-acyl- α -amino amides can provide the corresponding amino acids and organic acids in excellent yields (Equation 8). This methodology presents a facile route to both natural and unnatural amino acids. The advantages of the newly developed methodology

are: (i) it avoids the use toxic cyanide that is used in Strecker method,³² (ii) it uses inexpensive ammonia over the more costly primary amines, and (iii) the purification of the products is achieved by simple recrystallization methods thus avoiding the use of chromatography.

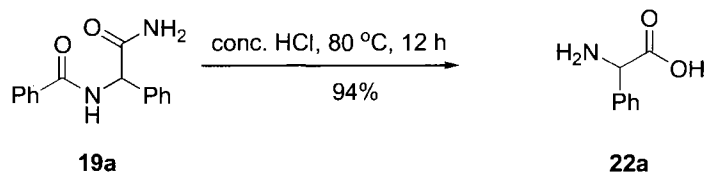
Equation 7



Scheme 3



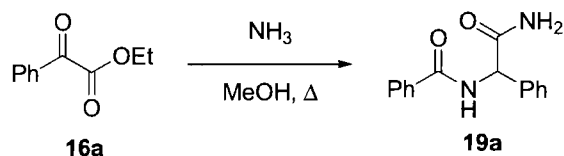
Equation 8



Optimization studies

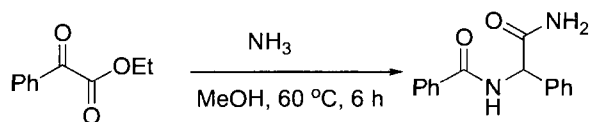
The optimization studies were carried out with α -keto ester **16a**. The influence of temperature on the reaction rate was studied by systematically varying temperature, and monitoring the reaction time effect on the isolated yields (Table 1). The reaction is quite slow near ambient temperatures. However, considerable acceleration of the reaction rates were observed at 60°C, and nearly quantitative conversions were obtained within 6 hours. Increasing the temperature to 90°C did not result in any noticeable change. It was later observed that the aliphatic substrates required higher temperatures and extended reaction times.

Table 1: Effect of reaction time and temperature on isolated yield



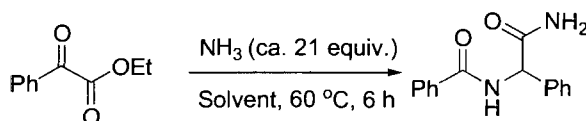
Entry	Temperature/°C	Time/h	Isolated Yield (%)
1	20	6	<10
2	20	18	13
3	35	6	15
4	35	18	29
5	50	6	63
6	50	18	80
7	60	6	90
8	60	18	82
9	90	6	84
10	90	18	68

The reaction was also found to be affected by the amount of ammonia used. A saturated solution of ammonia, estimated to be around 21 equivalences, was required to give optimal conversions (Table 2).

Table 2: Effect of equivalence of ammonia on the isolated yield

Entry	Equivalence of Ammonia	Isolated Yield (%)
1	3	9
2	7	17
3	14	49
4	21	90

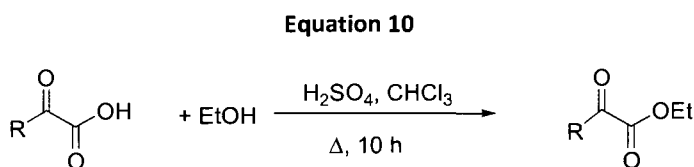
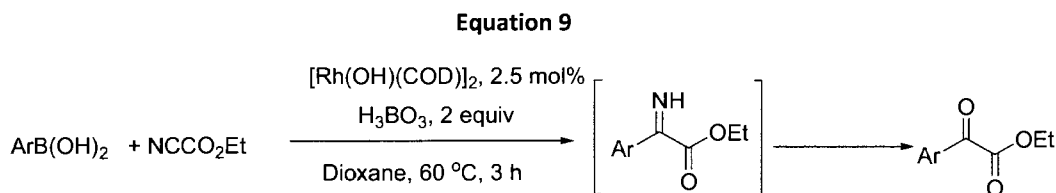
The study of reaction in different solvents revealed that alcohols (methanol and ethanol), were the solvents of choice (Table 3). This fact could be attributed to the higher solubility of the reactants in these alcoholic solvents. Aqueous conditions and other polar and nonpolar solvents gave poor conversions in comparison to ethanol and methanol.

Table 3: Effect of solvent on the isolated yield

Entry	Solvent	Isolated Yield (%)
1	H ₂ O	29
2	MeOH	90
3	EtOH	84
4	PhCH ₃	<10
5	DMSO	<10
6	THF	24
7	DME	34

Synthesis of α -keto esters from boronic acid reagents

In order to study the scope of application of this reaction further, we required access to a variety of α -keto esters. A number of aryl α -keto esters were synthesized from aryl boronic acids according to the procedure reported by Shimizu and coworkers.³⁹ This methodology uses a rhodium catalyst to couple organoboronic acid reagents and ethyl cyanofornate to form α -imino ethyl esters that ultimately hydrolyze to form α -keto ethylesters (Equation 9).³⁹ An alternative method is the acid catalyzed esterification of α -keto acids (Equation 10).⁴⁰



Scope of application

The reaction is effective for a wide range of starting α -keto esters including aliphatic, aryl and heteroaryl variants. Functional groups such as nitro and halides were also tolerated under the optimized conditions. Under these conditions, aryl α -keto esters with varying steric demand and electronic properties reacted well to afford the product with good to excellent yields (Table 4). X-ray quality crystals of N-acyl α -amino amide **19h** variant (Figure 2) and of the heteroaryl **19k** were grown and the crystal structures solved by both Ben Cooper and Dr. Charles Macdonald. The crystal structure of **19k** shows disorder in the thiophene rings, estimated to be 75% for the thiophene next to the keto group and 50% for the other (Figure 3).

The reactivity of the aliphatic α -keto esters, however, was found to be sluggish. The reaction with these substrates necessitated an increase of the temperature and reaction time for satisfactory conversions. Good yields were obtained at 80 °C for 12 h reaction time (Table 5).

Figure 2: Ortep structure of 19h, thermal ellipsoids shown at 50% probability, H atoms omitted for clarity

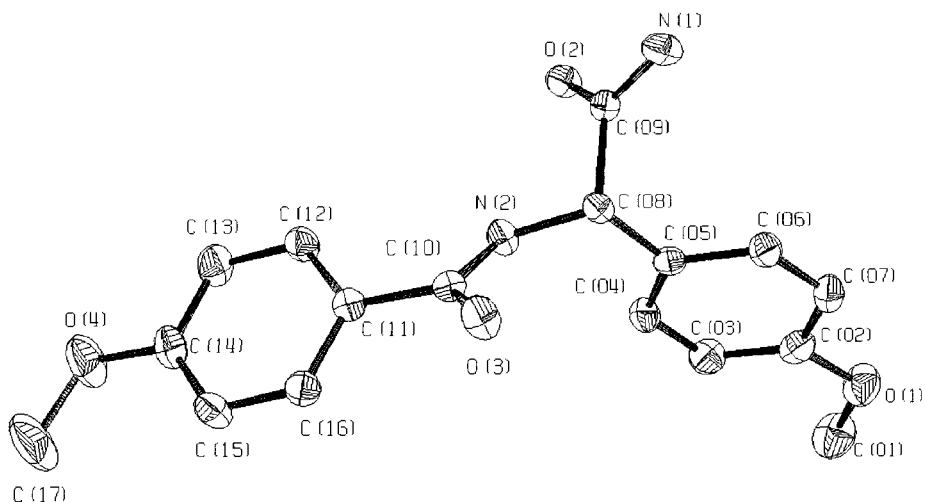


Figure 3: Ortep structure of 19k, at 50% ellipsoid probability select atoms labelled for clarity (thiophene rings are disordered to some extent)

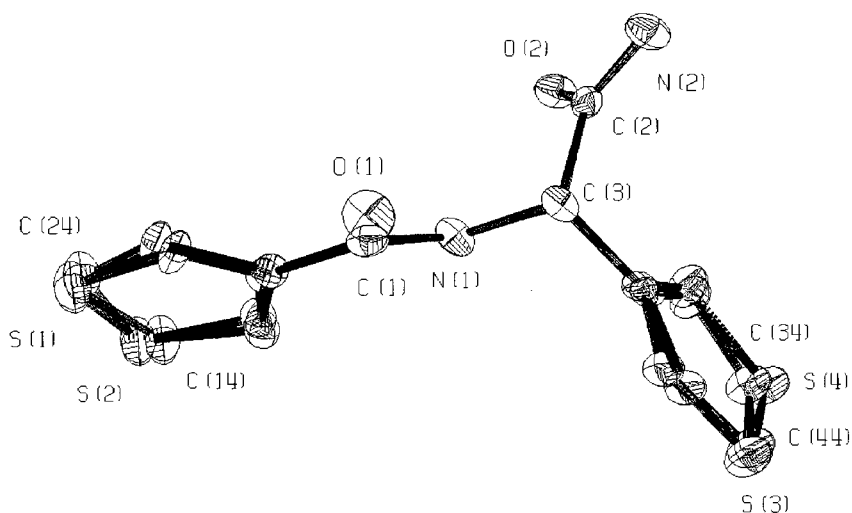


Table 4: Reaction of aryl and heteroaryl α -keto esters with ammonia

Entry	R	Isolated Yield (%)
1	Ph	90
2	2-CH ₃ C ₆ H ₄	84
3		88
4	2-BrC ₆ H ₄	84
5	3-MeOC ₆ H ₄	86
6	3-O ₂ NC ₆ H ₄	81
7	4-FC ₆ H ₄	92
8	4-MeOC ₆ H ₄	95
9	1-Naphthyl	91
10	2-Naphthyl	91
11		93

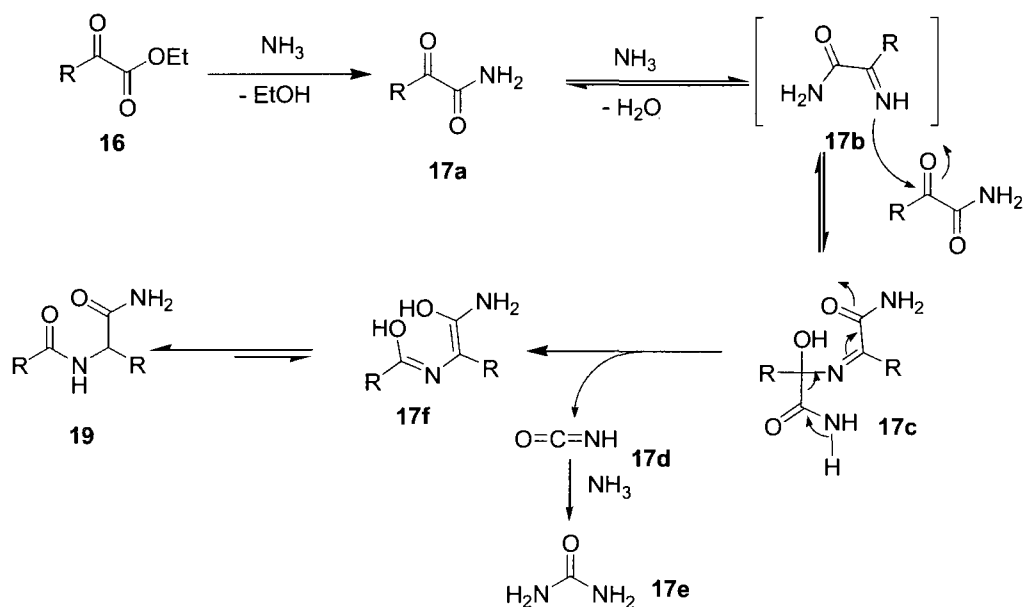
Table 5: Reactivities of aliphatic α -keto esters with ammonia

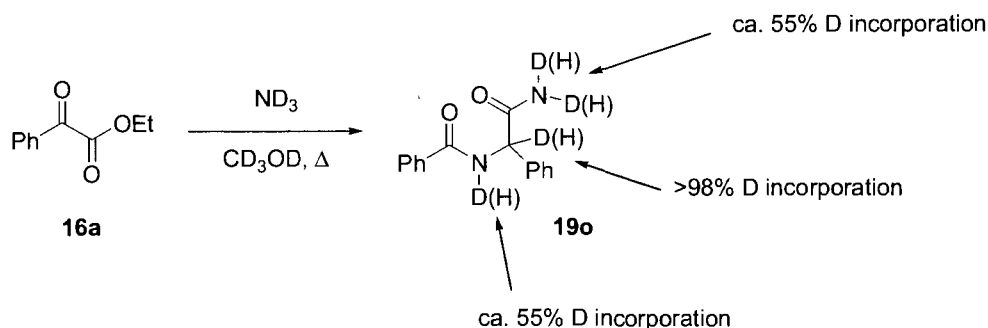
Entry	R	Isolated Yield (%)
1	CH ₃	80
2	(CH ₃) ₂ CH	75
3	PhCH ₂	80

Proposed mechanism and supporting studies

We briefly studied the mechanism of the newly discovered methodology. Aminolysis of the α -keto ester **16** to form the α -keto amide **17a** is believed to be the first step. This is usually the major product when the reaction is stopped prematurely. The α -keto amide **17a** then reacts with a second molecule of ammonia to form the α -imino amide **17b** which in turn reacts with the intermediate **17a**, to form **17c**. Isocyanide **17c** is then believed to be extruded to form **17f**. This hypothesis is supported by the detection of a small amount of urea **17e** in the ^1H NMR of the crude product. The urea **17e** is believed to have formed via the reaction of isocyanide **17d** with ammonia. Furthermore, we conducted the labelling studies, using both deuterated ammonia and deuterated methanol, in order to support the formation of **17f** and its tautomerization to N-acyl- α -amino amide product **19**. The nearly complete incorporation of deuterium at the α -position is observed, while the 55% deuterium incorporation at the nitrogen atoms may be due to post-isolation deuterium hydrogen exchange due to adventitious water (Scheme 5).

Scheme 4: Proposed mechanism



Scheme 5: Deuterium (D) labelling experiment

Conclusion

In conclusion, we have developed a methodology for the direct and facile synthesis of a variety of N-acyl- α -amino amides in one step from α -keto esters. The desired products were obtained in good to excellent yields through simple precipitation or recrystallization from the crude reaction mixture, and did not require any further purification. N-acyl- α -amino amides are also easily converted to the corresponding α -amino acids. Therefore, this new methodology constitutes a novel practical way to synthesize unnatural α -amino acids. The pre-existing literature also highlights the usefulness of N-acyl- α -amino amides as starting materials for the synthesis of drug like compounds.

3. Experimental

3.1. α -keto esters

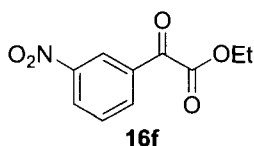
3.1.1. Synthesis

α -Keto esters were prepared by exactly following the procedure developed by Shimizu and Murakami:³⁹ A solution of the aryl boronic acid (0.60 mmol, 1.2 equiv), H_2BO_2 (1.00 mmol, 2.0 equiv), $[\text{Rh}(\text{OH})(\text{cod})]_2$ (0.0125 mmol, 2.5 mol%) and ethyl cyanoformate (0.5

mmol, 1.0 equiv) in 1,4dioxane (1.0 mL) was stirred for 30 min at rt and then at 60 °C for 3 h under argon. The reaction mixture was then cooled to rt and diluted with EtOAc (10 mL) and citric acid (10% in water, 5.0mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic extracts was washed with water (5 mL), brine (5 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to afford the crude α -keto ester, which was subsequently purified by silica gel chromatography (hexanes/EtOAc).

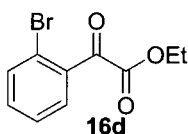
3.1.2. Characterization

- Ethyl 3-nitrobenzoylformate (**16f**)



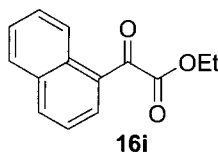
16f isolated as a yellow oil: ¹H NMR [CDCl₃, 300 MHz] δ 8.86 (1H, s), 8.50 (1H, d, *J* = 8.1 Hz), 8.39 (1H, d, *J* = 8.1), 7.78-7.72 (1H, dd, *J* = 8.1, 8.1Hz), 4.48 (2H, q, *J* = 7.2 Hz), 1.44 (3H, t, *J* = 7.2); ¹³C NMR (CDCl₃, 75 MHz) δ 183.63, 162.25, 148.49, 135.58, 134.01, 130.34, 128.94, 125.04, 63.15, 14.12.

- Ethyl 2-bromobenzoylformate (**16d**)



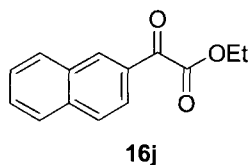
16d isolated as a brown oil: ¹H NMR [C₆D₆, 500 MHz] δ 7.41 (1H, d, *J* = 7.7 Hz), 7.07 (1H, d, *J* = 7.7 Hz), 6.67 (1H, m), 6.57 (1H, m), 3.98 (2H, q, 7.2 Hz), 0.88 (3H, t, *J* = 7.2 Hz); ¹³C NMR [C₆D₆, 75 MHz] δ 187.43, 162.88, 136.29, 133.60, 131.81, 130.18, 130.02, 121.71, 62.48, 18.62.

- Ethyl 1-naphthoylformate (**16i**)



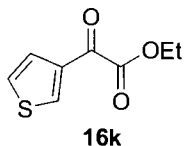
16i isolated as a pale yellow solid: m.p. = 79-82 °C; ^1H NMR [CDCl_3 , 300 MHz] δ 9.04 (1H, d, J = 8.4 Hz), 8.13 (1H, d, J = 8.1 Hz), 7.96 (1H, d, J = 7.1 Hz), 7.93 (1H, d, J = 8.1 Hz), 7.73-7.68 (1H, m), 7.63-7.54 (2 H, m), 4.53-4.46 (2H, q, J = 7.1 Hz), 1.47-1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR [CDCl_3 , 75 MHz] δ 188.9, 164.67, 135.83, 134.04, 133.92, 131.09, 129.31, 128.80, 128.40, 127.10, 125.71, 124.36, 62.43, 14.20.

- Ethyl 2-naphthoylformate (**16j**)



16j isolated as a dark brown oil: ; ^1H NMR (CDCl_3 , 300 MHz) δ 8.55 (1H, s), 8.04 (1H, d, J = 8.7 Hz), 7.97-7.85 (3H, m), 7.76-7.53 (2H, m), 4.52 (2H, q, J = 7.2 Hz), 1.46 (3H, t, J = 7.2 Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 186.46, 164.06, 136.44, 133.57, 132.35, 130.08, 129.90, 129.67, 129.03, 128.01, 127.26, 124.03, 62.50, 14.26.

- Ethyl thiophene-3-oyl formate (**16k**)



16k isolated as a yellow oil; ^1H NMR (C_6D_6 , 300 MHz) δ 8.14 (1H, dd, J = 1 Hz, 2.9 Hz), 7.53 (1H, dd, J = 1 Hz, 5.1 Hz), 6.50 (1H, dd, J = 2.9, 5.1 Hz), 3.89 (2H, q, J = 7.1 Hz), 0.87 (3H, t, J = 7.1 Hz); ^{13}C NMR (C_6D_6 , 75 MHz) δ 182.13, 162.97, 138.24, 137.21, 125.21, 124.59, 61.96, 13.35.

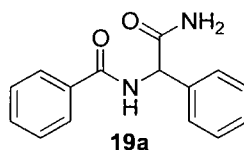
3.2. N-acyl- α -amino amides

3.2.1. Synthesis

To a solution of ammonia in methanol (*ca.* 7M in MeOH, 3.0 mL, *ca.* 21 equiv.) in a Swagelock 50 mL stainless steel cylinder or an Ace pressure tube was added the α -keto ester (1.00 mmol). The cylinder (or tube) was sealed and heated in an oil bath at 60 °C or 80 °C for 6 h or 12 h respectively. The cylinder (or tube) was then removed and allowed to cool to room temperature (1 h), and then cooled further in a -40 °C bath. The Swagelock cylinder (or pressure tube) was opened and the contents were transferred to a small Erlenmeyer flask (50 mL). A steady stream of air was blown over the reaction mixture until some precipitation was observed. The reaction mixture was then heated slightly to redissolve all solid matter, and allowed to stand at room temperature for 2 h. The precipitated product was filtered off through a sintered glass funnel, and washed with ice-cold methanol (*ca.* 5 mL).

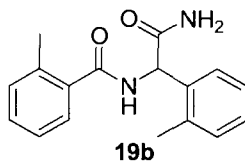
3.2.2. Characterization

- **N-(2-Amino-2-oxo-1-phenylethyl)benzamide**



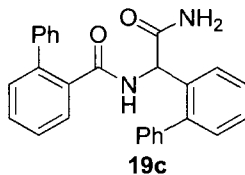
19a isolated as a white solid: m.p. = 199-201 °C (MeOH); ^1H NMR [(CD₃)₂SO, 500 MHz] δ 8.70 (1H, d, J = 8.0 Hz), 7.91 (2H, d, J = 7.0 Hz), 7.90 (1H, br s), 7.57 – 7.50 (3H, m), 7.46 (2H, t, J = 7.5 Hz), 7.36 (2H, t, J = 7.5 Hz), 7.30 (1H, t, J = 7.5 Hz), 7.24 (1H, br s), 5.63 (1H, d, J = 8.0 Hz); ^{13}C NMR (CD₃OD, 75 MHz) δ 172.16, 166.42, 139.30, 134.47, 131.89, 128.72 (two signals overlapped), 128.10, 127.98 (two signals overlapped), 56.42; IR (KBr) ν 3372, 3321, 3169, 3056, 1698, 1650 cm⁻¹; HRMS (EI) m/z calcd. for C₁₅H₁₄N₂O₂ (M⁺) 254.1055, found 254.1057.

- **N-[2-Amino-1-(2-methylphenyl)-2-oxoethyl]-2-methylbenzamide**



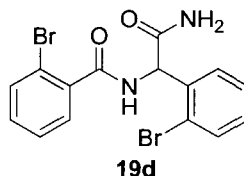
19b isolated as a white solid: m.p. = 205-207 °C (MeOH); ^1H NMR $[(\text{CD}_3)_2\text{SO}, 500 \text{ MHz}]$ δ 8.62 (1H, d, $J = 8.0 \text{ Hz}$), 7.48 (1H, br s), 7.43 – 7.28 (3H, m), 7.25 – 7.13 (6H, m), 5.74 (1H, d, $J = 8.0 \text{ Hz}$), 2.44 (3H, s), 2.32 (3H, s); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}, 75 \text{ MHz}]$ δ 172.06, 168.69, 136.75, 136.60 (two signals overlapped), 135.35, 130.24, 130.14, 129.29, 127.58, 127.52, 127.35, 125.86, 125.28, 53.70, 19.38, 19.11; IR (KBr) ν 3431, 3284, 1680, 1629 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ (M^+) 282.1368, found 282.1366.

- **N-[2-Amino-1-(biphenyl-2-yl)-2-oxoethyl]biphenyl-2-carboxamide**



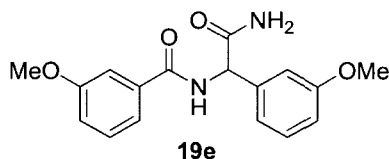
19c isolated as a white solid: m.p. = 108-109 °C (MeOH); ^1H NMR $[(\text{CD}_3)_2\text{SO}, 300 \text{ MHz}]$ δ 8.78 (1H, d, $J = 7.5 \text{ Hz}$), 7.55 – 7.15 (19H, m), 6.83 (1H, br s), 5.42 (1H, d, $J = 7.5 \text{ Hz}$); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}, 75 \text{ MHz}]$ δ 172.03, 168.39, 141.85, 140.41, 140.01, 139.35, 136.26, 135.32, 129.89, 129.75, 129.45, 129.21, 128.35, 128.28, 128.08, 128.04, 127.90, 127.51, 127.43, 127.06, 126.97, 126.79, 54.21; IR (KBr) ν 3430, 3253, 3057, 1689, 1631 cm^{-1} ; HRMS (EI) m/z calcd. For $\text{C}_{27}\text{H}_{22}\text{N}_2\text{O}_2$ (M^+) 406.1681, found 406.1684.

- **N-[2-Amino-1-(2-bromophenyl)-2-oxoethyl]-2-bromobenzamide**



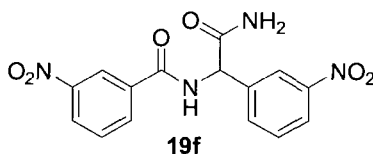
19d isolated as a white solid: m.p. = 181-183 °C (MeOH); ^1H NMR (CD_3OD , 300 MHz) δ 7.70 -7.15 (11H, m), 6.05 (1H, s); ^{13}C NMR (CD_3OD , 75 MHz) δ 173.49, 169.91, 138.77, 137.47, 134.14, 134.06, 132.23, 130.99, 130.53, 130.00, 128.86, 128.37, 125.43, 120.33, 58.41; IR (KBr) ν 3433, 3304, 1669, 1621 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{15}\text{H}_{12}\text{Br}^{79}_2\text{N}_2\text{O}_2$ (M^+) 409.9266, found 409.9261.

- **N-[2-Amino-1-(3-methoxyphenyl)-2-oxoethyl]-3-methoxybenzamide**



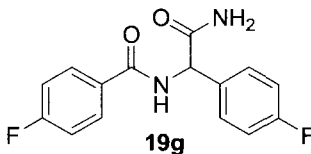
19e isolated as a white solid: m.p. = 144-146 °C (MeOH); ^1H NMR (CD_3OD , 300 MHz) δ 7.47 -7.25 (4H, m), 7.13 – 7.05 (3H, m), 6.93 – 6.87 (1H, m), 5.64 (1H, s) [N-H signals absent]; ^{13}C NMR (CD_3OD , 75 MHz) δ 175.02, 169.61, 161.60, 161.42, 140.60, 136.69, 130.97, 130.83, 121.10, 120.78, 119.02, 115.02, 114.57, 113.92, 59.03, 56.03, 55.88; IR (KBr) ν 3303, 3154, 1697, 1630 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4$ (M^+) 314.1267, found 314.1266.

- **N-[2-Amino-1-(3-Nitrophenyl)-2-oxoethyl]-3-nitrobenzamide**



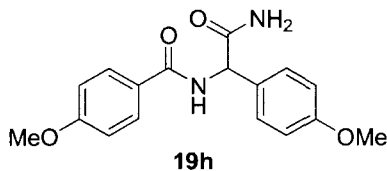
19f isolated as a white solid: m.p. = 178-179 °C (MeOH); ^1H NMR $[(\text{CD}_3)_2\text{SO}, 300 \text{ MHz}]$ δ 9.55 (1H, d, $J = 8.0 \text{ Hz}$), 8.78 (1H, t, $J = 2.0 \text{ Hz}$), 8.46 (1H, t, $J = 2.0 \text{ Hz}$), 8.40 – 8.25 (2H, m), 8.20 (1H, dt, $J = 8.0, 2.0 \text{ Hz}$), 8.00 (1H, d, $J = 8.0 \text{ Hz}$), 7.93 (1H, br s), 7.82 – 7.62 (2H, m), 7.43 (1H, br s), 5.84 (1H, d, $J = 8.0 \text{ Hz}$); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}, 75 \text{ MHz}]$ δ 170.60, 164.34, 147.74, 147.63, 140.69, 135.13, 134.70, 134.37, 129.99, 129.90, 126.15, 122.71, 122.65, 122.53, 56.41; IR (KBr) ν 3310, 3150, 1698, 1635, 1606, 1535, 1348 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_6$ (M^+) 344.0757, found 344.0760.

• ***N*-[2-Amino-1-(4-fluorophenyl)-2-oxoethyl]-4-fluorobenzamide**



19g isolated as a white solid: m.p. = 202-204 °C (MeOH); ^1H NMR $[(\text{CD}_3)_2\text{SO}, 300 \text{ MHz}]$ δ 8.72 (1H, d, $J = 7.5 \text{ Hz}$), 7.87 (2H, app t, $J = 7.5 \text{ Hz}$), 7.60 (1H, br s), 7.44 (2H, app t, $J = 7.5 \text{ Hz}$), 7.30 – 7.00 (5H, m), 5.50 (1H, d, $J = 7.5 \text{ Hz}$); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}, 75 \text{ MHz}]$ δ 171.59, 165.03, 164.47 (d, $J = 182 \text{ Hz}$), 161.21 (d, $J = 177 \text{ Hz}$), 134.96, 134.93, 130.43 (d, $J = 9 \text{ Hz}$), 129.67 (d, $J = 8 \text{ Hz}$), 115.20 (d, $J = 6.5 \text{ Hz}$), 114.92 (d, $J = 6.5 \text{ Hz}$), 56.21; IR (KBr) ν 3425, 3338, 1699, 1637 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{N}_2\text{O}_2$ (M^+) 290.0867, found 290.0869.

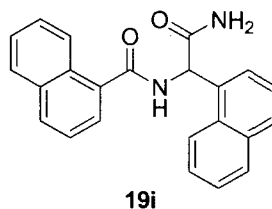
• ***N*-[2-Amino-1-(4-methoxyphenyl)-2-oxoethyl]-4-methoxybenzamide**



19h isolated as a clear, colourless, crystalline solid: m.p. = 253-255 °C (MeOH); ^1H NMR $[(\text{CD}_3)_2\text{SO}, 300 \text{ MHz}]$ δ 8.48 (1H, d, $J = 8.0 \text{ Hz}$), 7.91 (2H, d, $J = 8.5 \text{ Hz}$), 7.63 (1H, br s), 7.44 (2H, d, $J = 8.5 \text{ Hz}$), 7.20 (1H, br s), 6.99 (2H, d, $J = 8.5 \text{ Hz}$), 6.92 (2H, d, $J = 8.5 \text{ Hz}$), 5.56 (1H, d, $J = 8.0 \text{ Hz}$), 3.80 (3H, s), 3.74 (3H, s); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}, 75 \text{ MHz}]$ δ 172.20, 165.28, 161.70,

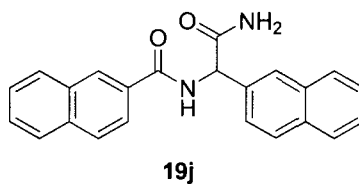
158.70, 130.98, 129.46, 128.74, 126.22, 113.63, 113.40 56.16, 55.33, 55.10; IR (KBr) ν 3365, 3321, 1696, 1646, 1622 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4$ (M^+) 314.1267, found 314.1267.

- ***N*-[2-Amino-1-(naphthalen-1-yl)-2-oxoethyl]-1-naphthamide**



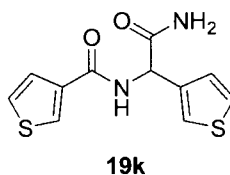
19i isolated as a white solid: m.p. = 245-247 °C (MeOH); ^1H NMR [$(\text{CD}_3)_2\text{SO}$, 300 MHz] δ 9.22 (1H, d, J = 8.0 Hz), 8.40 – 8.28 (2H, m), 8.05 – 7.90 (4H, m), 7.81 (1H, br s), 7.75 – 7.42 (9H, m), 6.54 (1H, d, J = 8.0 Hz); ^{13}C NMR [$(\text{CD}_3)_2\text{SO}$, 75 MHz] δ 171.99, 168.19, 134.16, 134.05, 133.41, 132.96, 131.26, 129.81, 129.73, 128.57, 128.24, 128.03, 126.50, 126.37, 126.03, 125.75, 125.70, 125.53, 125.41, 125.27, 124.74, 123.57, 53.65; IR (KBr) ν 3445, 3286, 1685, 1633 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_2$ (M^+) 354.1368, found 354.1367.

- ***N*-[2-Amino-1-(naphthalen-2-yl)-2-oxoethyl]-2-naphthamide**



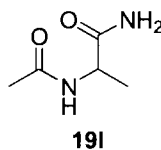
19j isolated as a white solid: m.p. = 230-232 °C (MeOH); ^1H NMR [$(\text{CD}_3)_2\text{SO}$, 300 MHz] δ 9.06 (1H, d, J = 7.0 Hz), 8.65 (1H, br s), 8.30 – 7.65 (10H, m), 7.60 – 7.25 (5H, m), 5.94 (1H, d, J = 7.0 Hz); ^{13}C NMR [$(\text{CD}_3)_2\text{SO}$, 75 MHz] δ 171.74, 166.10, 136.39, 134.27, 132.75, 132.46, 132.12, 131.25, 128.93, 128.00, 127.89, 127.80 (2 signals overlapped), 127.68, 127.61, 127.55, 126.70, 126.38, 126.32, 126.09, 125.89, 124.55, 57.17; IR (KBr) ν 3301, 3142, 1678, 1645 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_2$ (M^+) 354.1368, found 354.1370.

- ***N*-[2-Amino-2-oxo-1-(thiophen-3-yl)ethyl]thiophene-3-carboxamide**



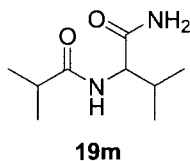
19k isolated as a clear, crystalline solid: m.p. = 216-218 °C (MeOH); ^1H NMR [(CD₃)₂SO, 300 MHz] δ 8.63 (1H, d, J = 8.5 Hz), 8.35 (1H, t, J = 1.0 Hz), 7.69 (1H, br s), 7.65 – 7.47 (4H, m), 7.28 – 7.22 (2H, m), 5.73 (1H, d, J = 8.5 Hz); ^{13}C NMR [(CD₃)₂SO, 75 MHz] δ 172.09, 162.13, 139.60, 137.62, 129.94, 127.87, 127.80, 126.97, 126.58, 123.28, 53.16; IR (KBr) ν 3386, 3276, 1678, 1633 cm⁻¹; HRMS (EI) m/z calcd. for C₁₁H₁₀N₂O₂S₂ (M⁺) 266.0184, found 266.081.

- **2-Acetamidopropanamide**



19l isolated as a clear, crystalline solid: m.p. = 157-159 °C (MeOH); ^1H NMR [(CD₃)₂SO, 300 MHz] δ 7.96 (1H, d, J = 7.5 Hz), 7.33 (1H, br s), 6.97 (1H, br s), 4.17 (1H, pentet, J = 7.5 Hz), 1.81 (3H, s), 1.15 (3H, d, J = 7.5 Hz); ^{13}C NMR [(CD₃)₂SO, 75 MHz] δ 174.78, 169.15, 48.04, 22.61, 18.36; IR (KBr) ν 3338, 3267, 1697, 1611 cm⁻¹; HRMS (EI) m/z calcd. for C₅H₁₀N₂O₂ (M⁺) 130.0742, found 130.0742.

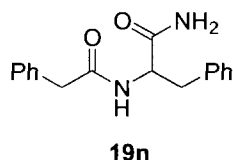
- **3-Methyl-2-[(2-Methylpropanoyl)amino]butanamide**



19m isolated as a white solid: m.p. = 175-177 °C (MeOH); ^1H NMR [(CD₃)₂SO, 300 MHz] δ 7.64 (1H, d, J = 9.0 Hz), 7.37 (1H, br s), 7.01 (1H, br s), 4.11 (1H, dd, J = 9.0, 7.0 Hz), 2.53

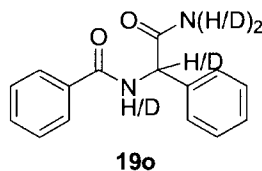
(1H, heptet, $J = 7.0$ Hz), 1.94 (1H, octet, $J = 7.0$ Hz), 0.99 (3H, d, $J = 7.0$ Hz), 0.96 (3H, d, $J = 7.0$ Hz), 0.84 (3H, d, $J = 7.0$ Hz), 0.82 (3H, d, $J = 7.0$ Hz); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}, 75 \text{ MHz}]$ δ 176.13, 173.34, 57.14, 33.63, 30.41, 20.07, 19.32, 19.25, 18.01; IR (KBr) ν 3335, 3270, 1690, 1638 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_{18}\text{N}_2\text{O}_2$ (M^+) 186.1368, found 186.1370.

- **3-Phenyl-2-(2-phenylacetamido)propanamide**



19n isolated as a white solid: m.p. = 204–206 °C (MeOH); ^1H NMR $[(\text{CD}_3)_2\text{SO}, 500 \text{ MHz}]$ δ 8.19 (1H, d, $J = 8.5$ Hz), 7.46 (1H, br s), 7.25 – 7.13 (8H, m), 7.09 (2H, d, $J = 7.5$ Hz), 7.05 (1H, br s), 4.46 (1H, app dt, $J = 9.0, 4.5$ Hz), 3.43 (1H, d, $J = 14.0$ Hz), 3.37 (1H, d, $J = 14.0$ Hz), 3.01 (1H, dd, $J = 13.5, 4.5$ Hz), 2.77 (1H, dd, $J = 13.5, 9.5$ Hz); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}, 75 \text{ MHz}]$ δ 173.10, 169.80, 137.98, 136.31, 129.18, 128.94, 128.00 (two signals overlapped), 126.15 (two signals overlapped), 53.76, 42.12, 37.73; IR (KBr) ν 3380, 3297, 1637 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ (M^+) 282.1368, found 282.1364.

- **N-(2-Amino-2-oxo-1-phenylethyl)benzamide – deuterated to some extent**

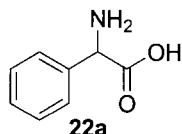


19o isolated as a white solid: m.p. = 178–180 °C (CD_3OD); ^1H NMR $[(\text{CD}_3)_2\text{SO}, 500 \text{ MHz}]$ δ 8.78 (0.45H, br s), 7.98 (2H, d, $J = 7.5$ Hz), 7.80 (0.45H, br s), 7.65 – 7.15 (8.45H, m), 5.72 (0.01H, m); ^{13}C NMR ($\text{CD}_3\text{OD}, 75 \text{ MHz}$) δ 171.87, 166.10, 138.77, 134.00, 131.53, 128.34 (two signals overlapped), 127.69 (two signals overlapped), 127.57, 56.61 (t, $J = 20$ Hz).

The deuterium incorporation at the α -position was calculated to be >98% by integrating the ^1H NMR signal at δ 5.72 versus the aromatic signals. The deuterium

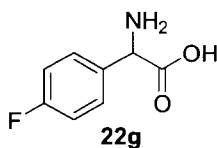
incorporation of the amide protons were calculated to be around 55% at both sites, by integrating the ^1H NMR signal at δ 8.78 or 7.80 versus the aromatic signals.

- **2-Amino-2-phenylacetic acid [2-Phenylglycine]**

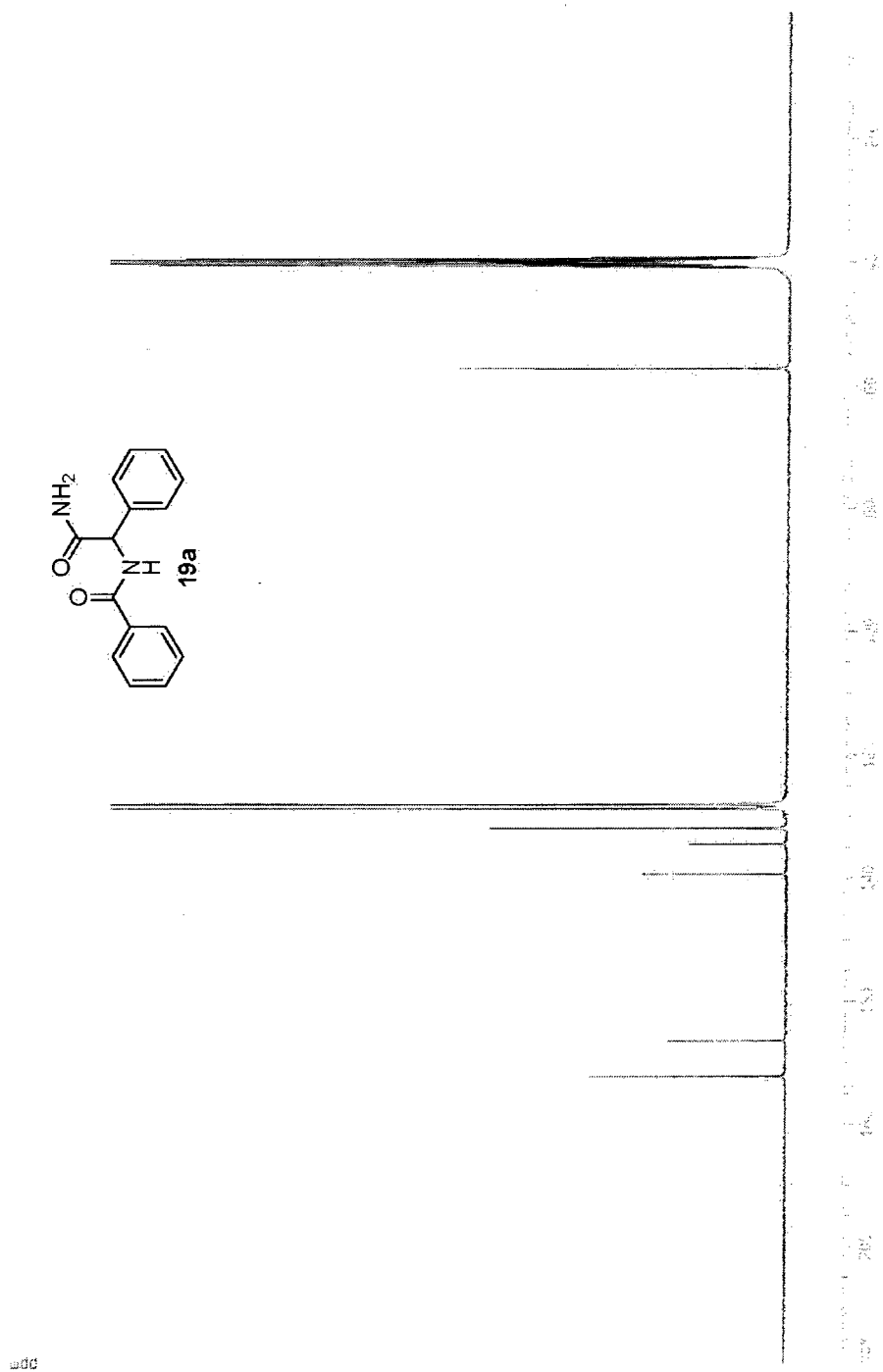


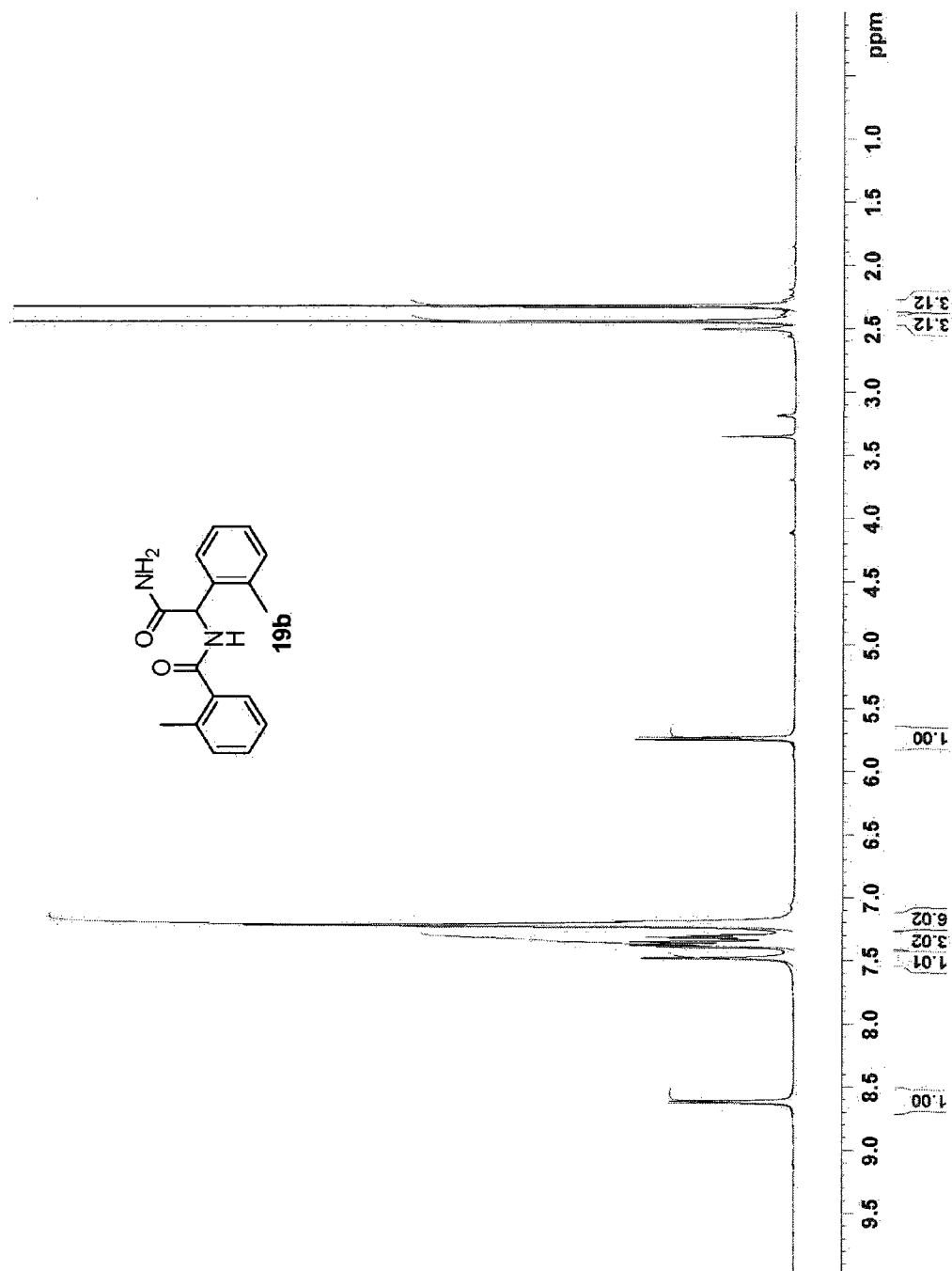
A solution of **2a** (254 mg, 1.00 mmol) in concentrated, aqueous HCl (1 mL) was refluxed for 12 h. The reaction mixture was cooled to room temperature and poured into a column containing Dowex 50W-X8 (15 mL, acid form, 50-100 mesh). The column first washed with 50% aqueous isopropanol (50 mL), and the water (50 mL). The amino acid was then eluted with aqueous ammonia (1 M). The eluent was collected and all volatiles were removed *in vacuo* to afford **22a** (130 mg, 94%) as a white solid. m.p. = 285-290 °C (H_2O); ^1H NMR [DCI/ D_2O /(CD_3) $_2\text{SO}$, 300 MHz] δ 8.10 (3H, s), 7.25 – 7.07 (5H, m), 4.80 (1H, s); ^{13}C NMR [DCI/ D_2O /(CD_3) $_2\text{SO}$, 75 MHz] δ 171.83, 133.97, 132.89, 132.13, 130.92, 58.55.

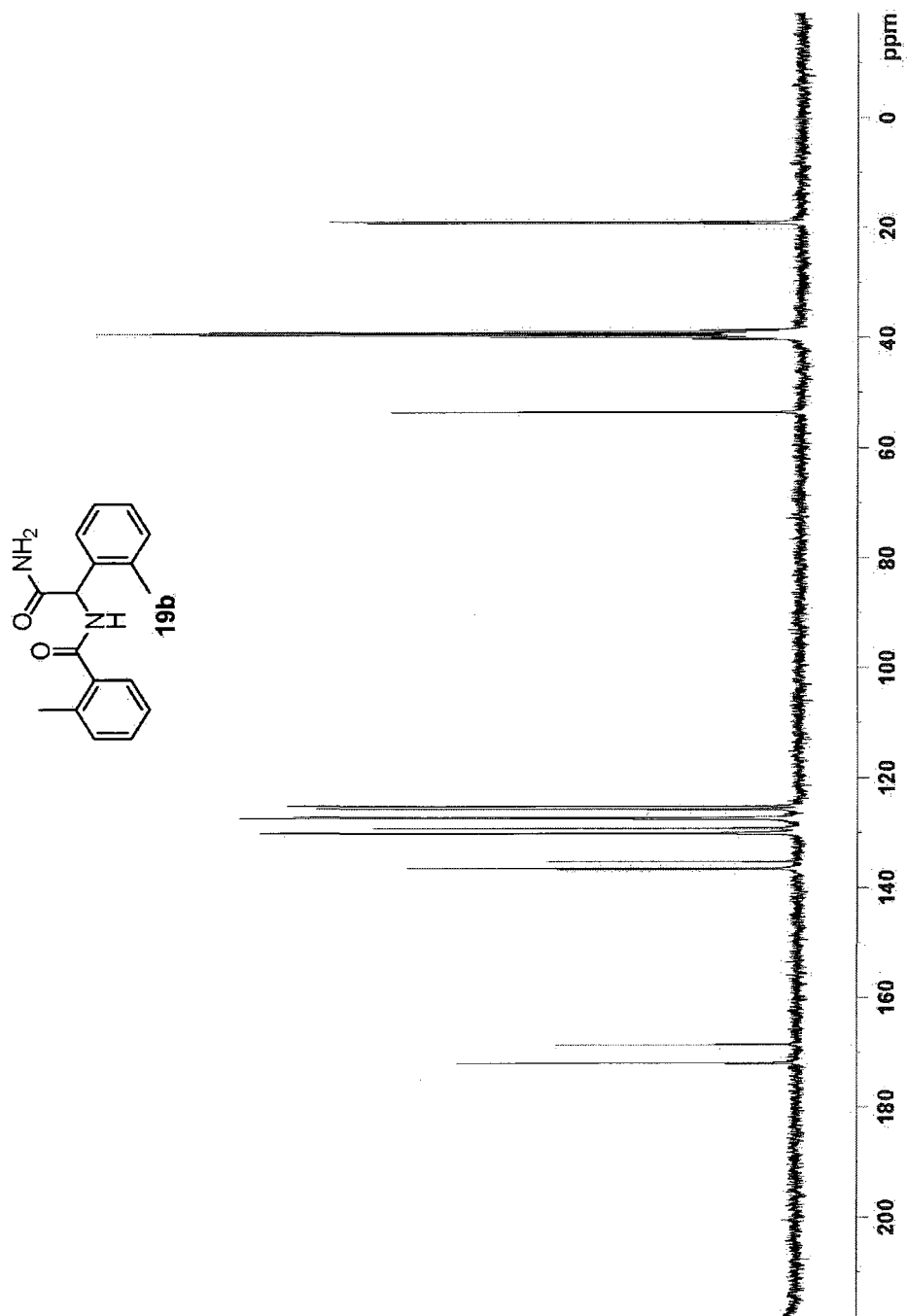
- **2-(4-Fluorophenyl)glycine**

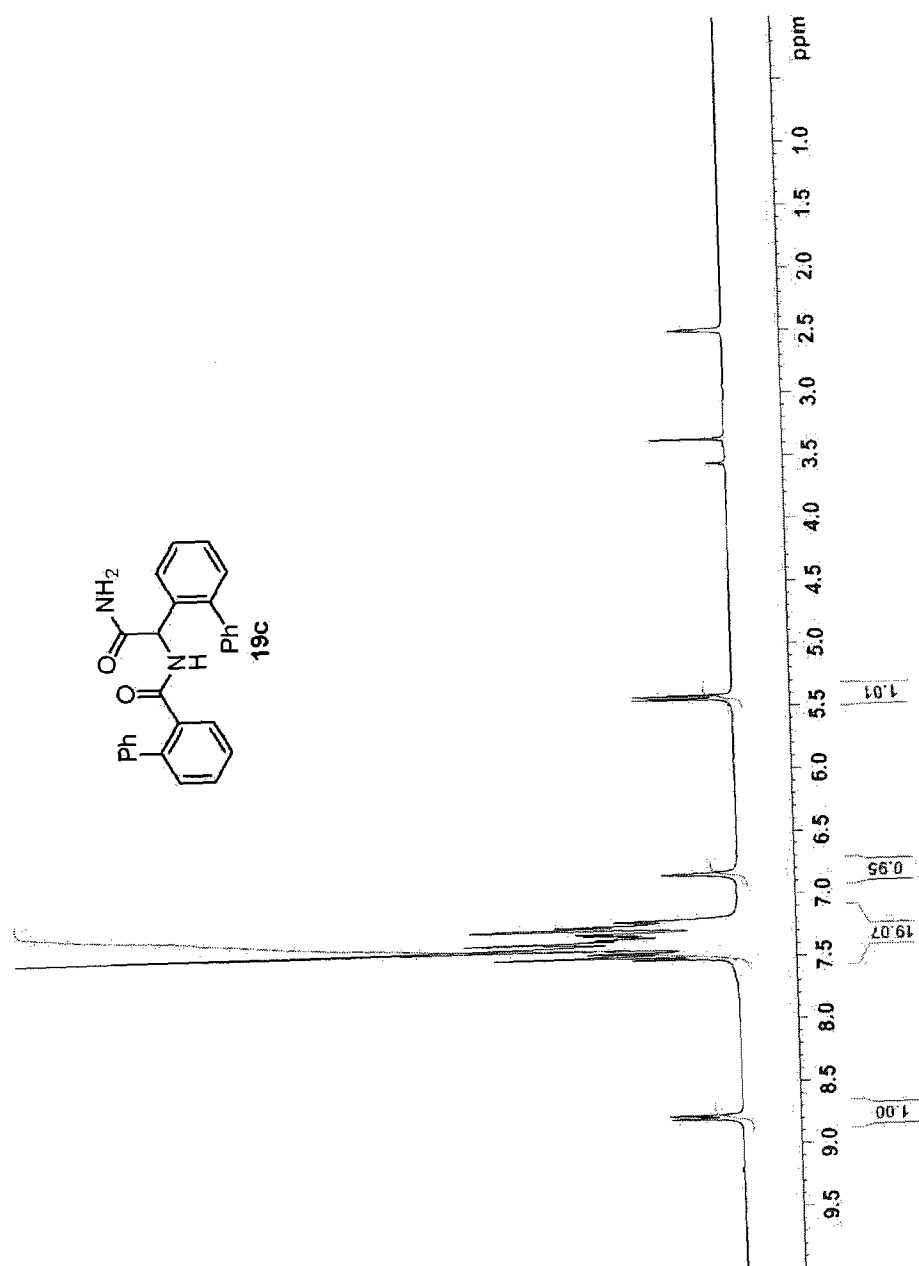


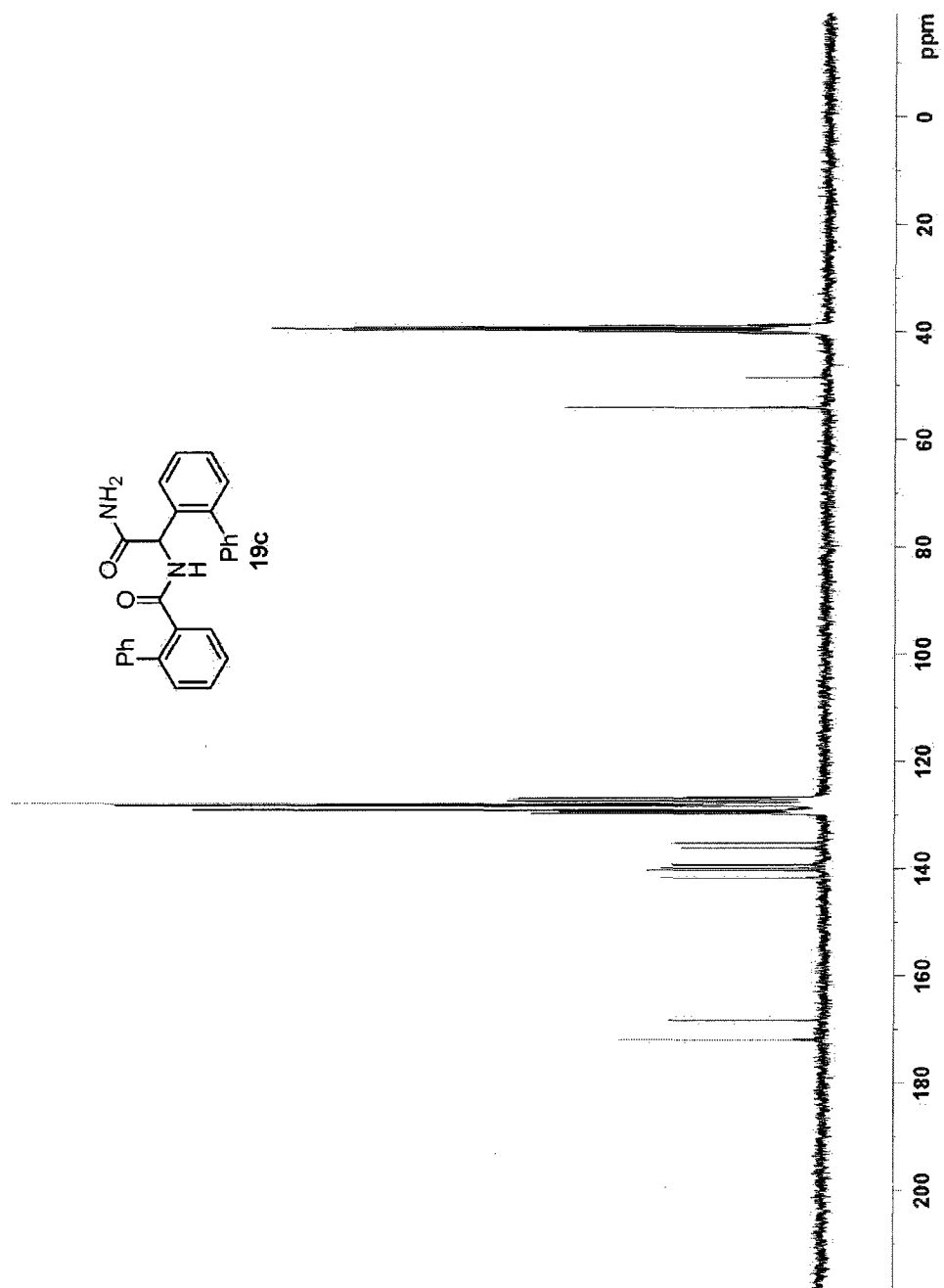
22g isolated as a white solid, ^1H NMR [DCI/ D_2O , 300 MHz] δ 7.35 – 7.16 (2H, m), 7.06-6.88 (2H, m), 4.82 (1H, s); ^{13}C NMR [DCI/ D_2O , 75 MHz] δ 171.31, 163.54, 133.11, 129.81, 118.72, 57.61.

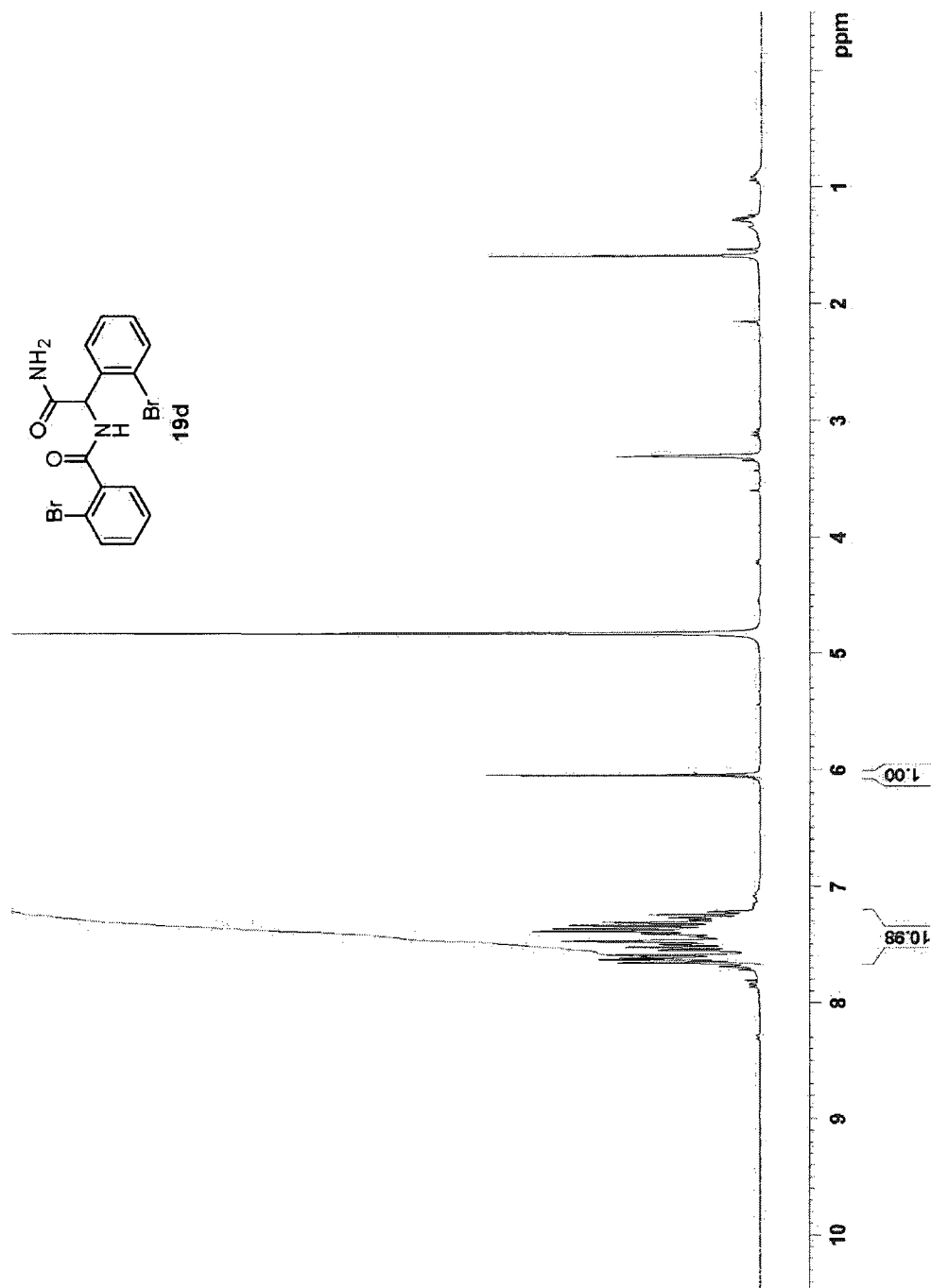


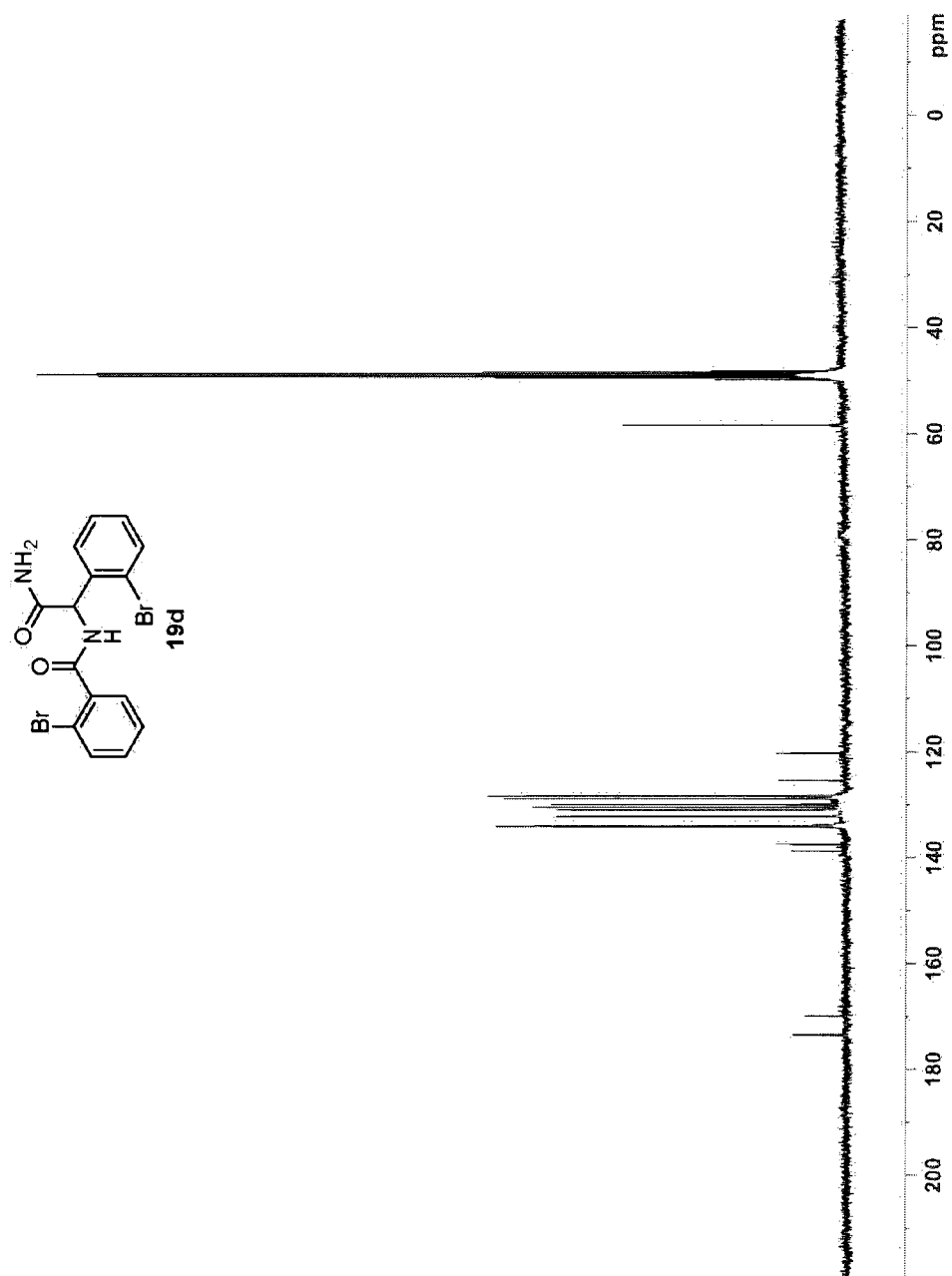


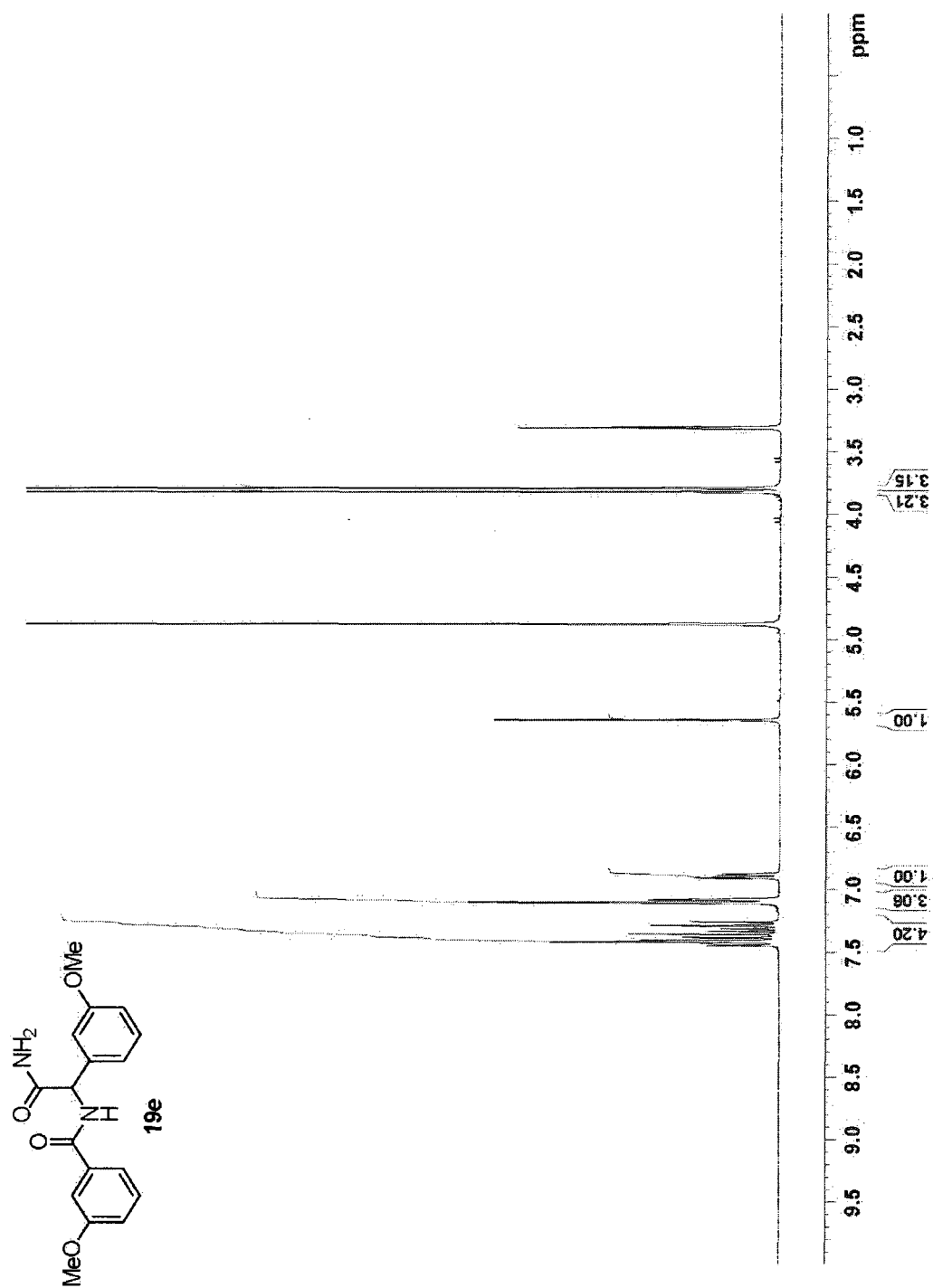


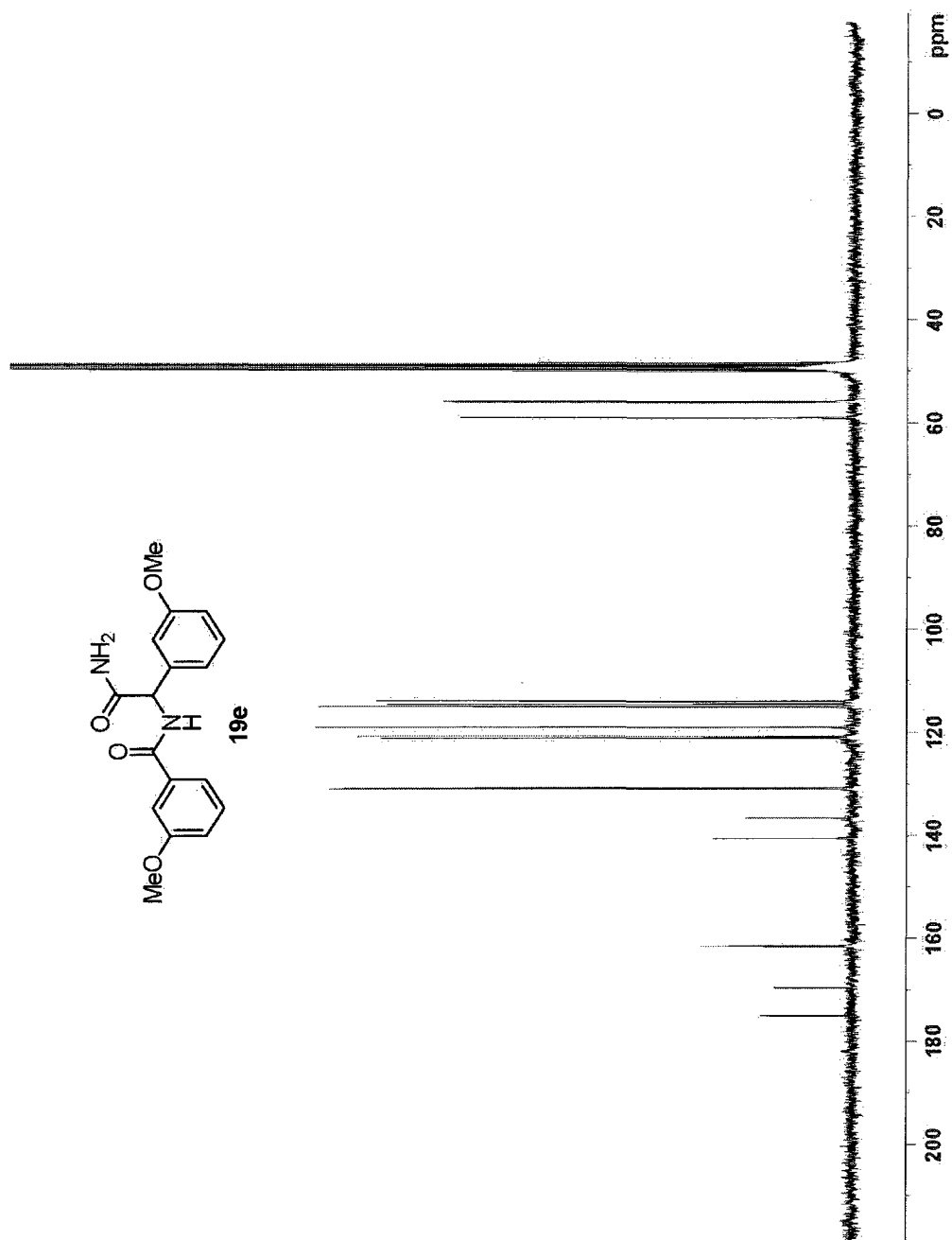


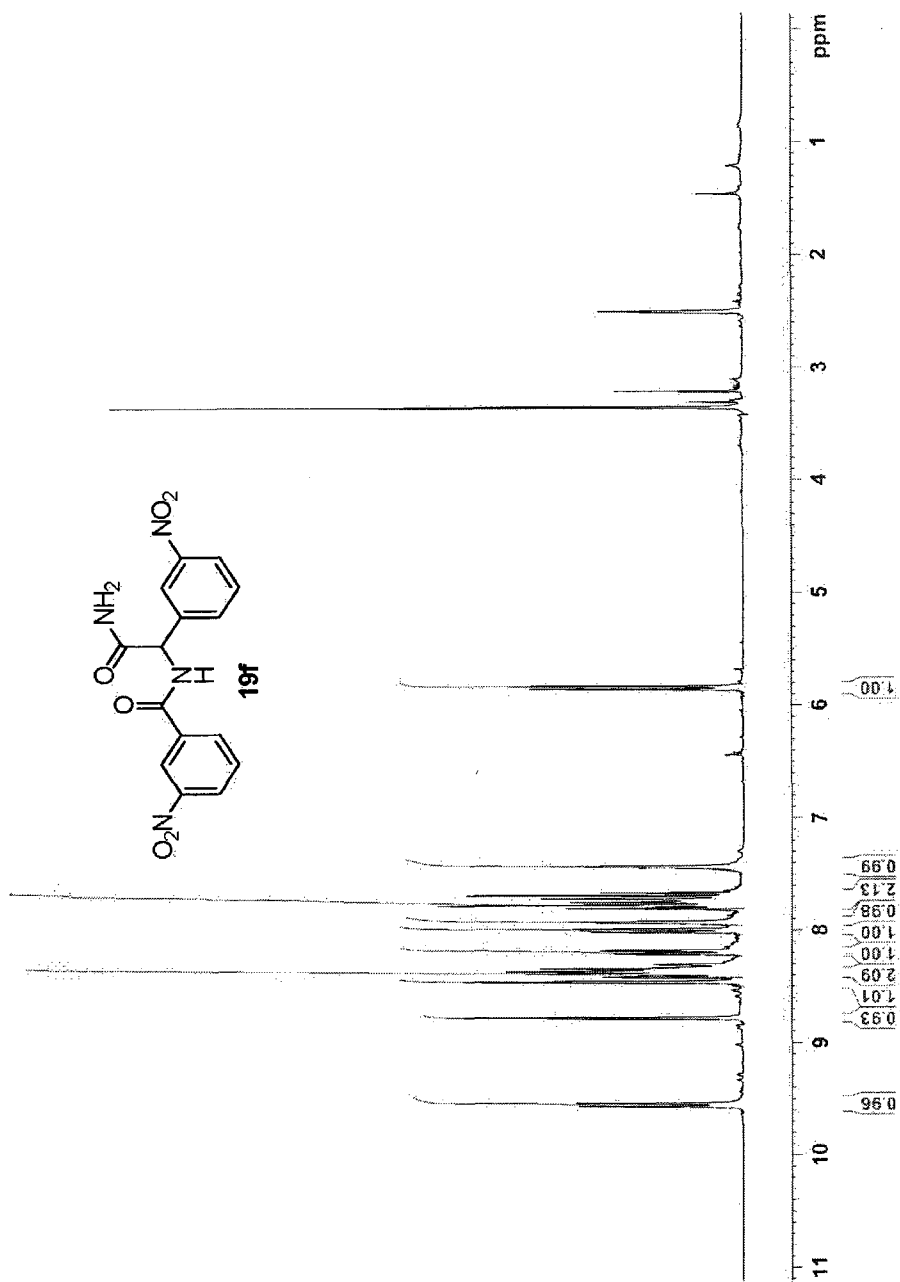


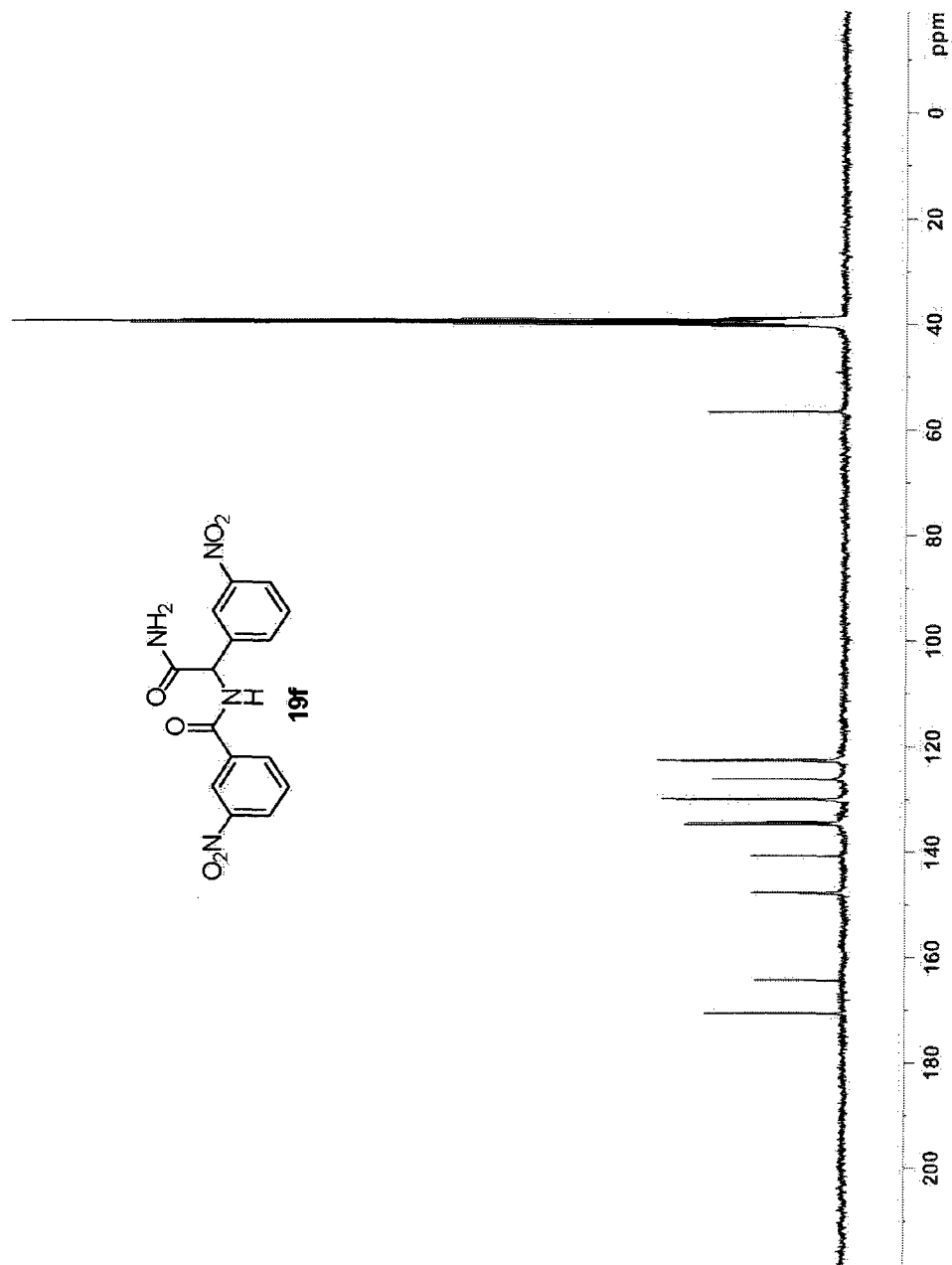


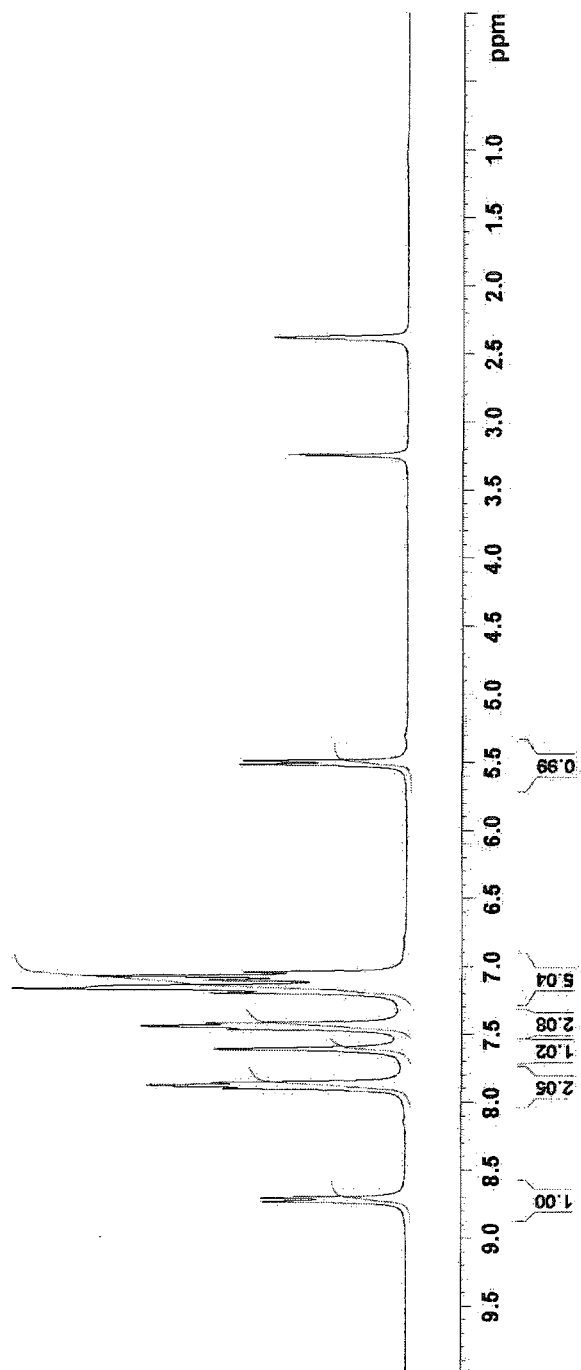
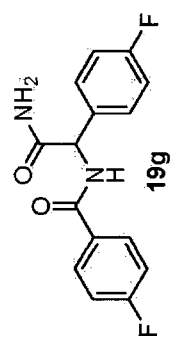


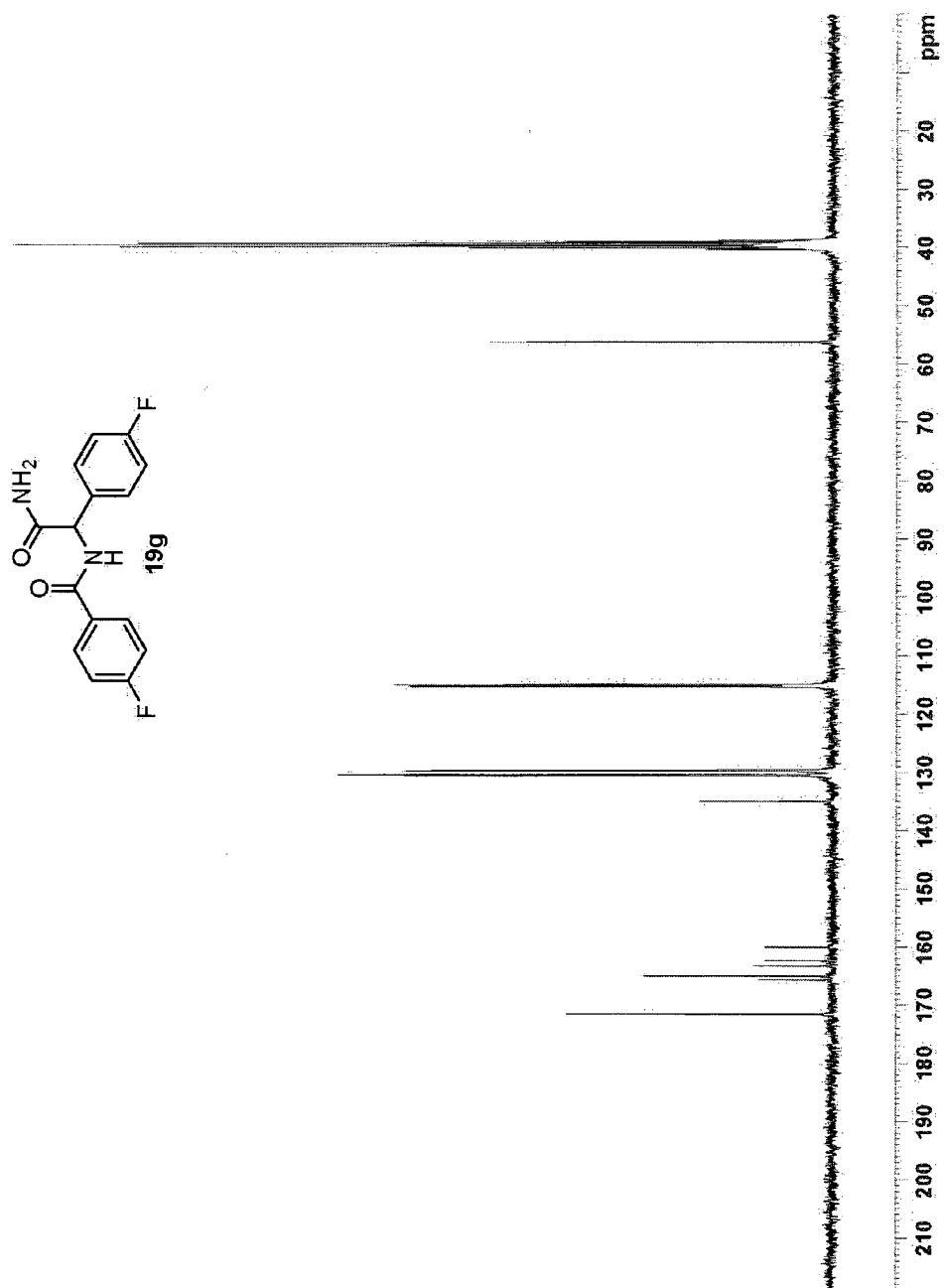


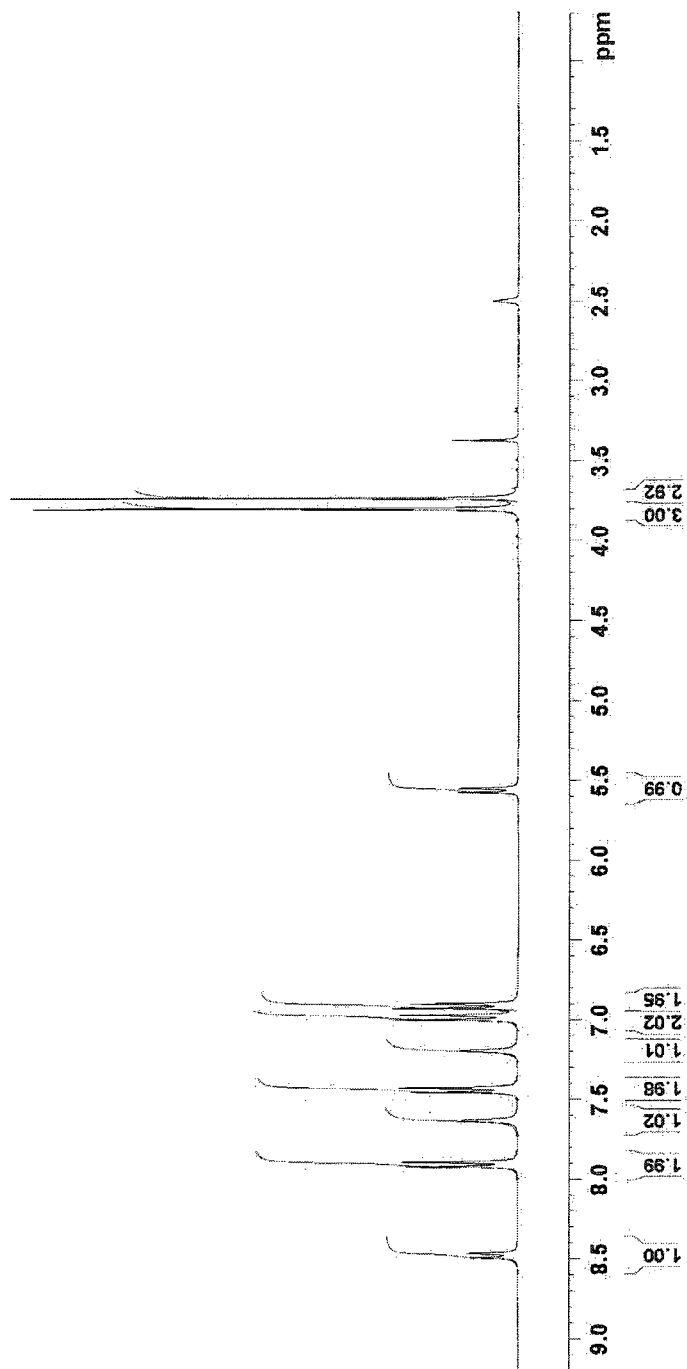
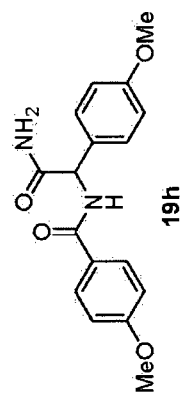


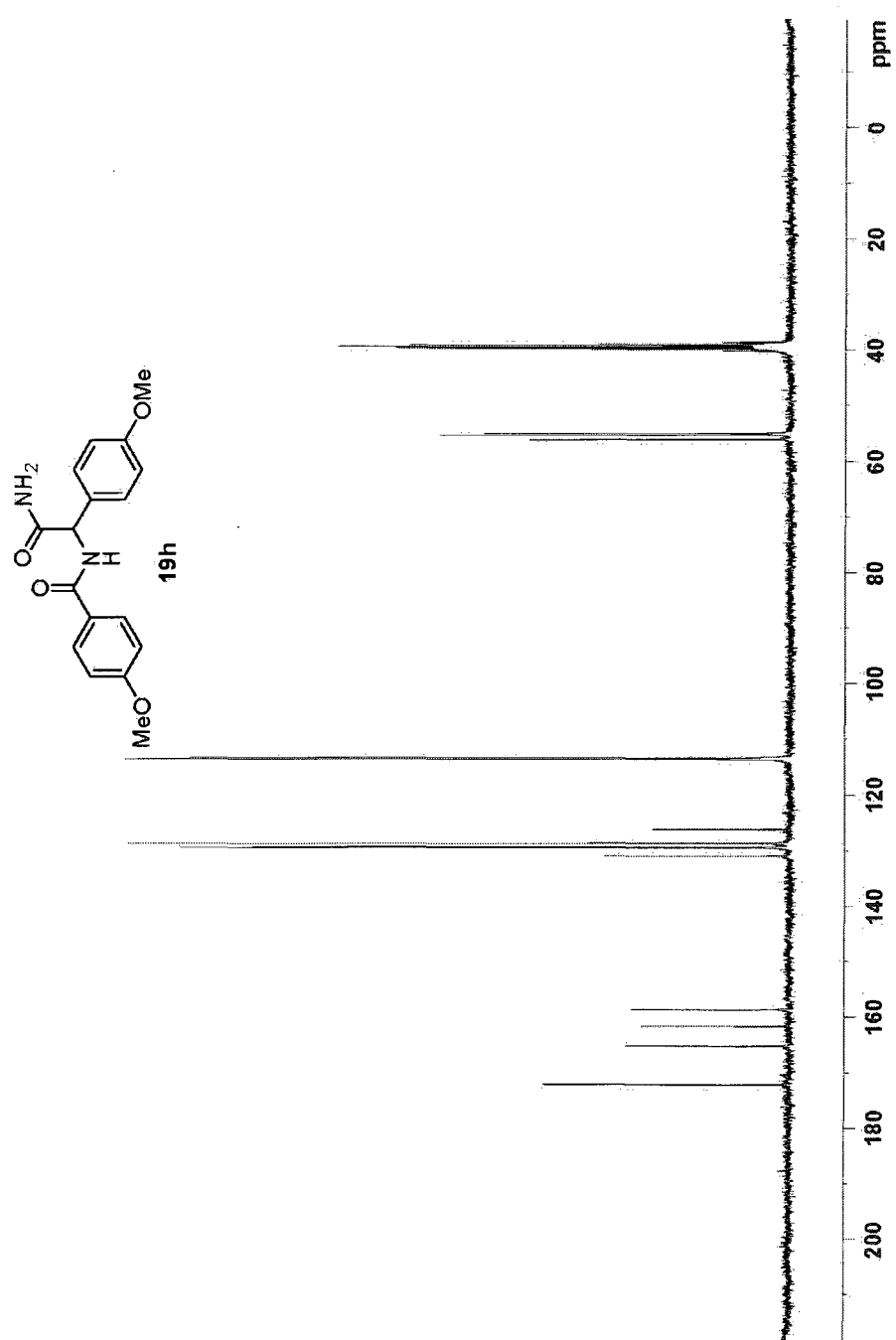


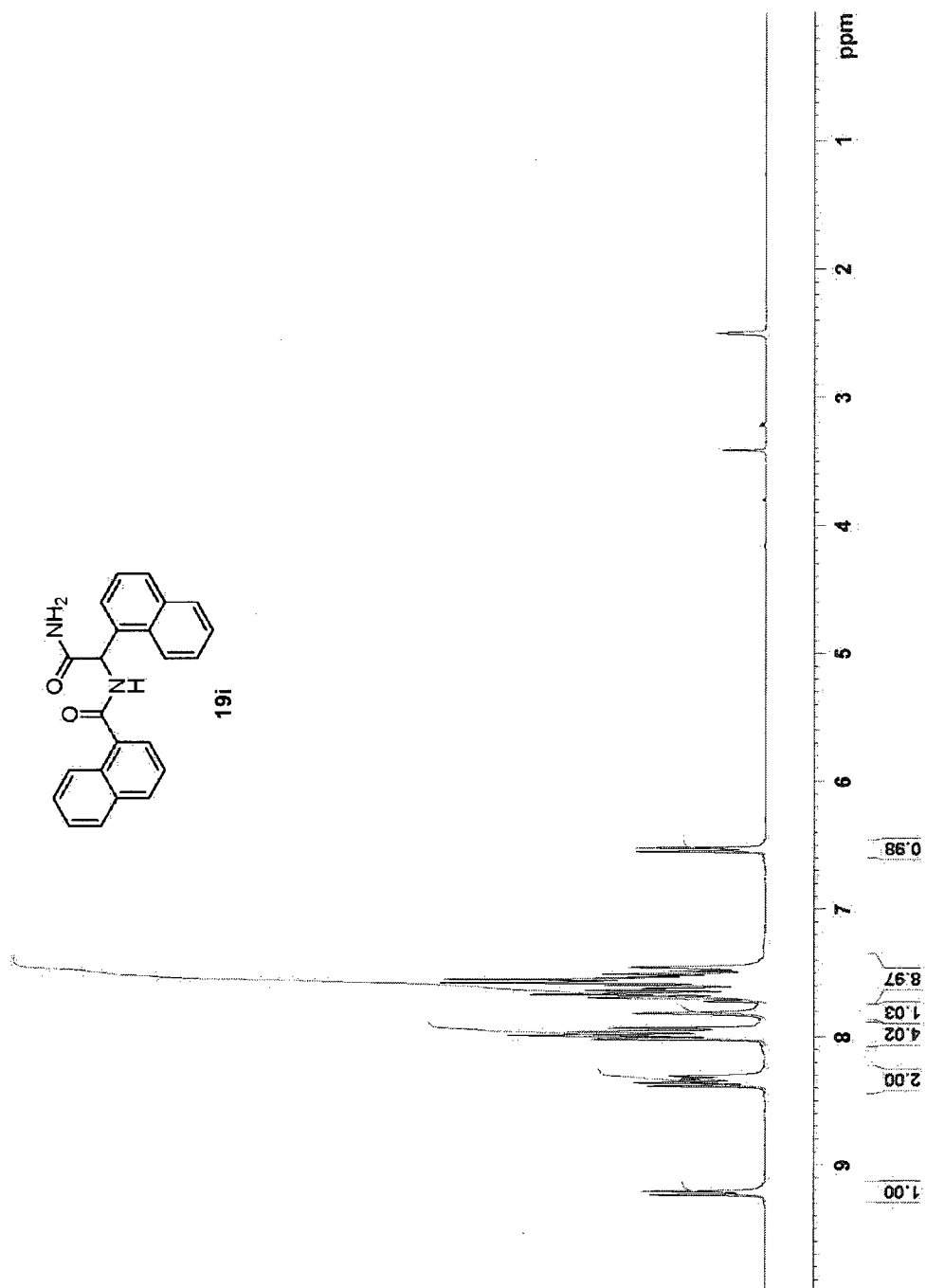


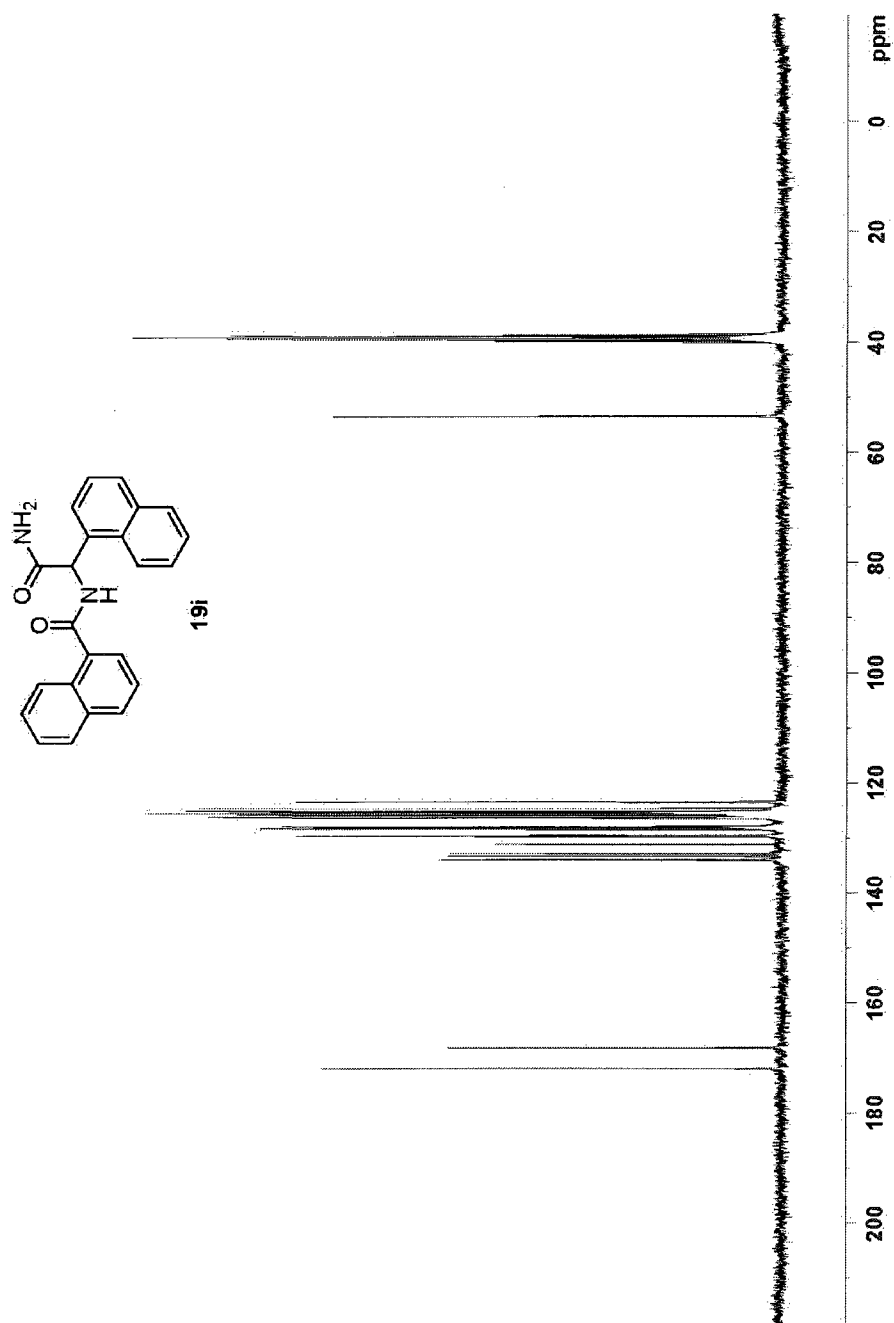


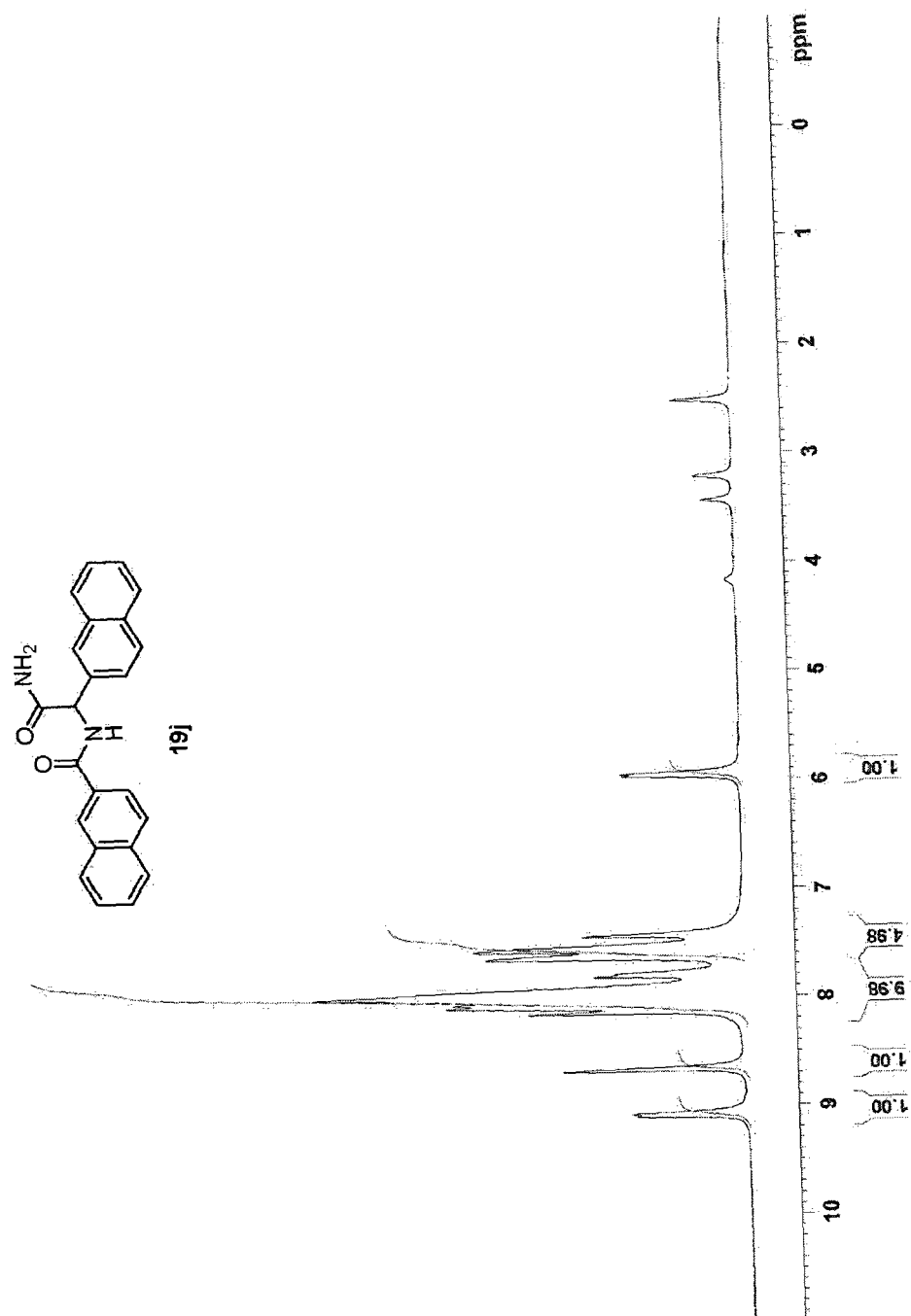


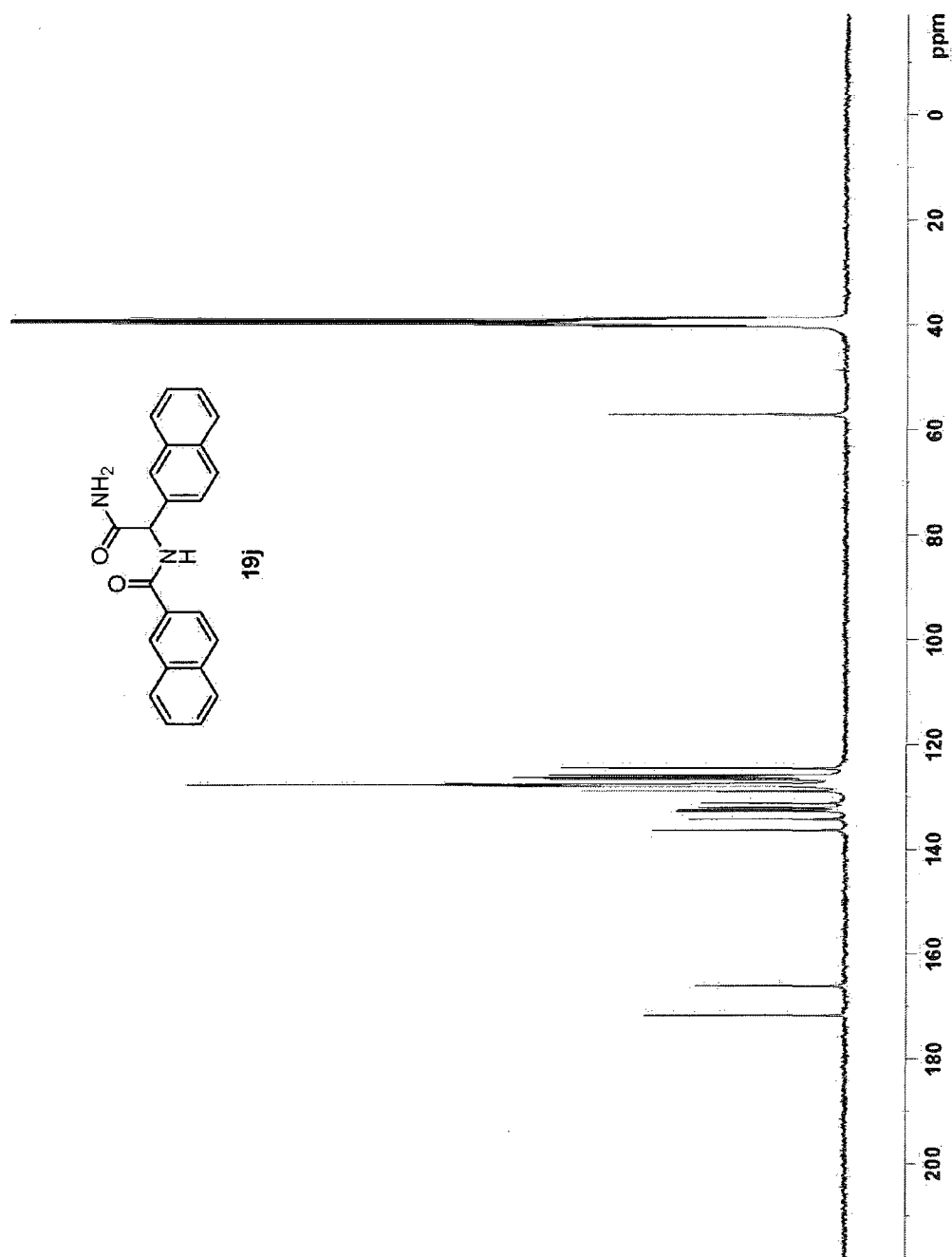


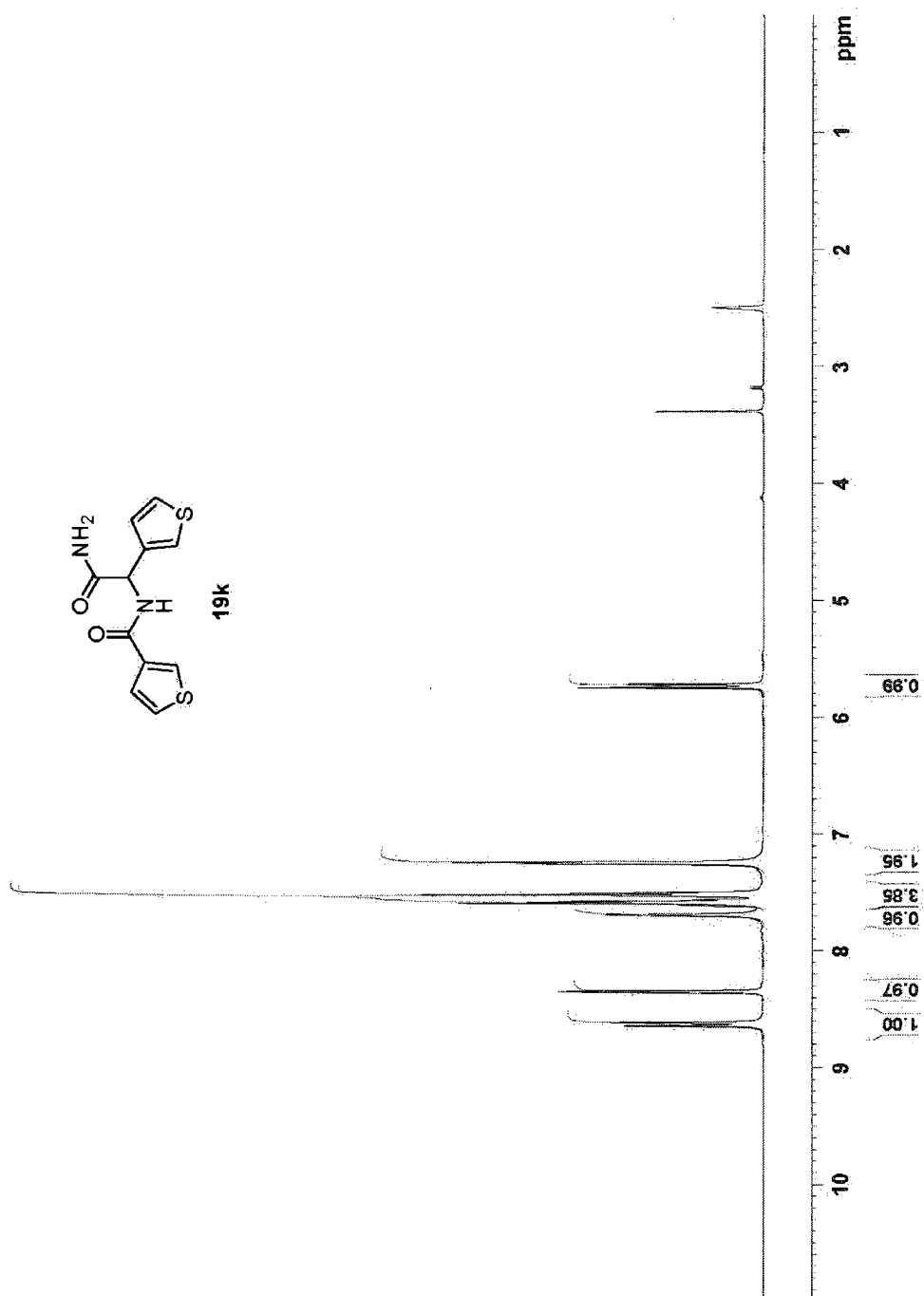


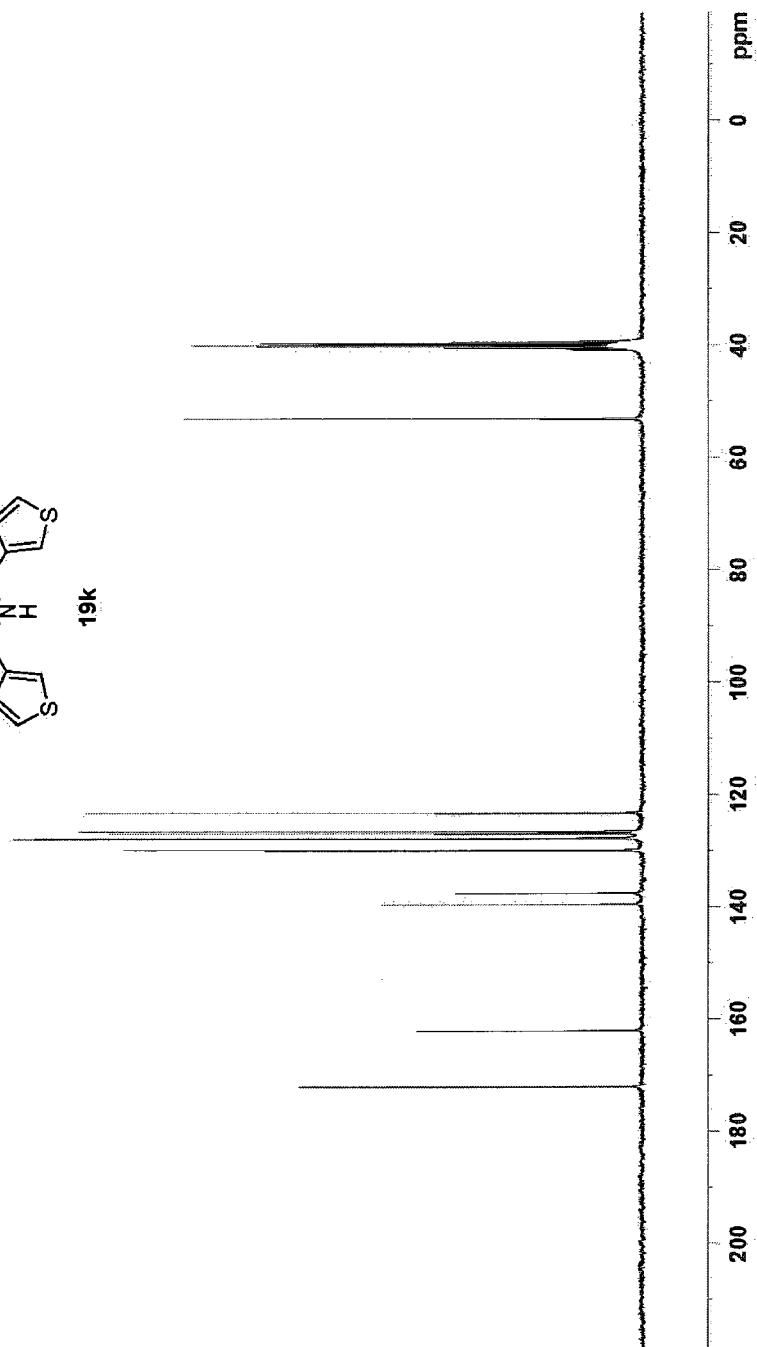
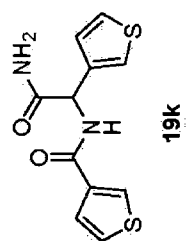


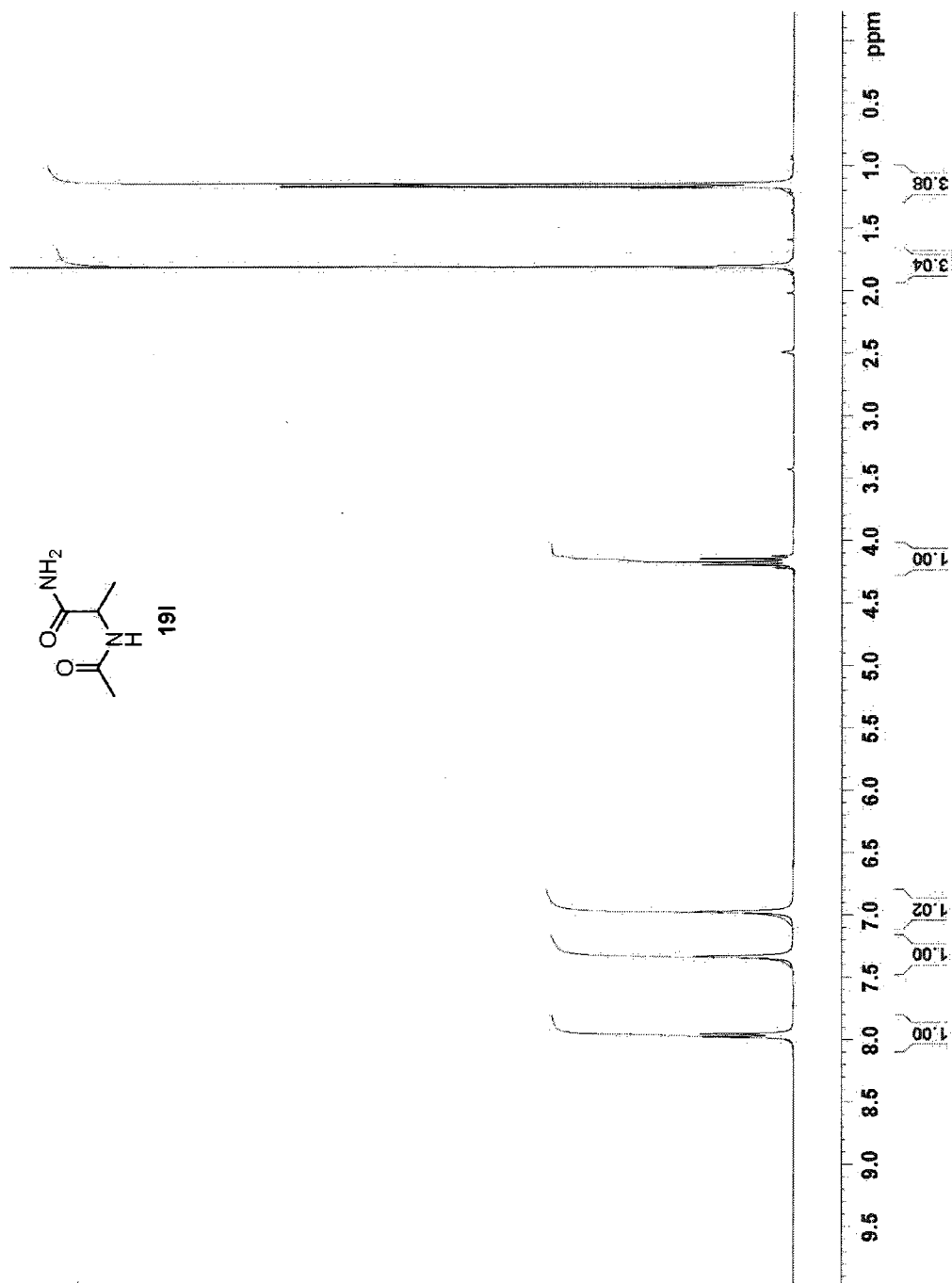
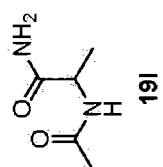


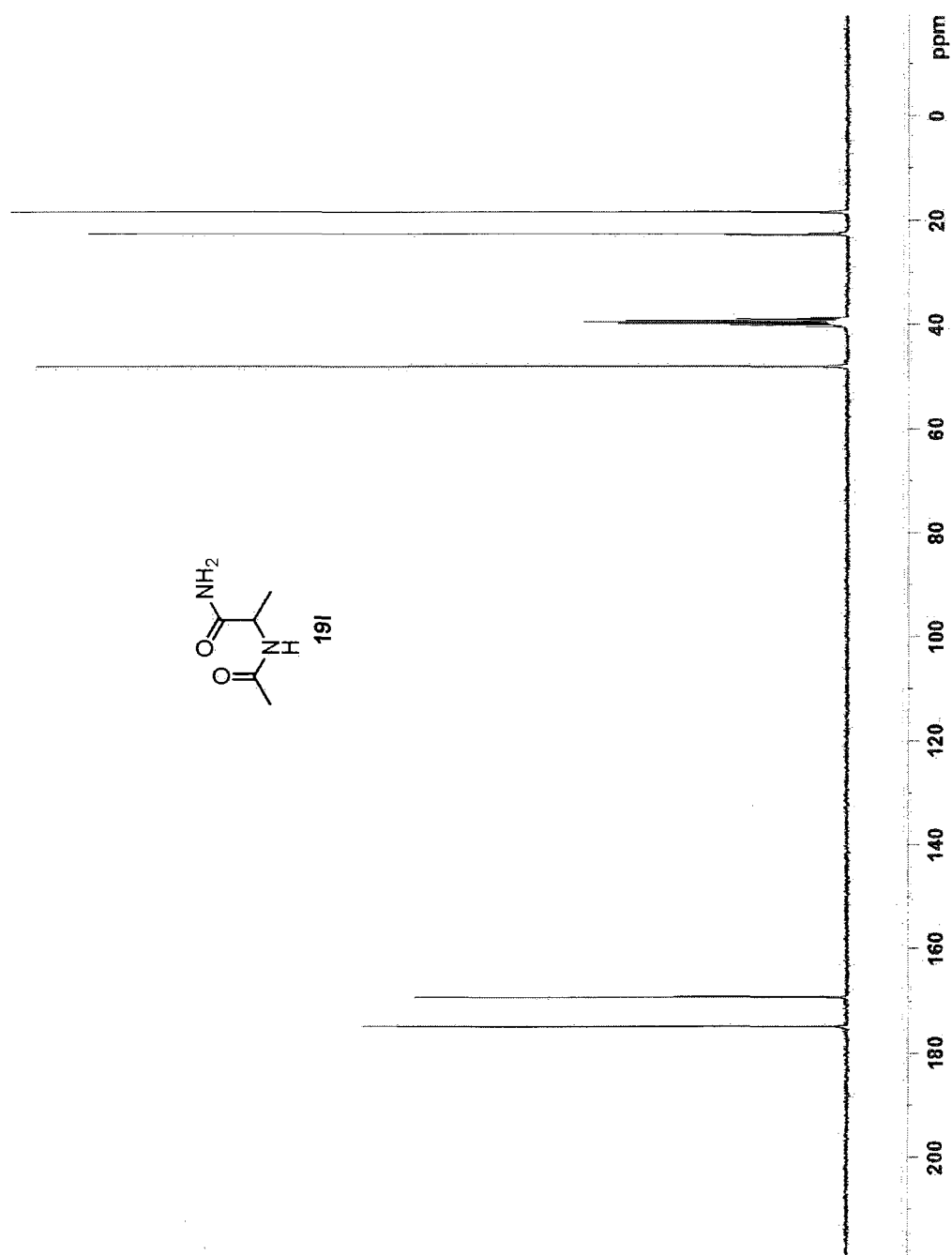


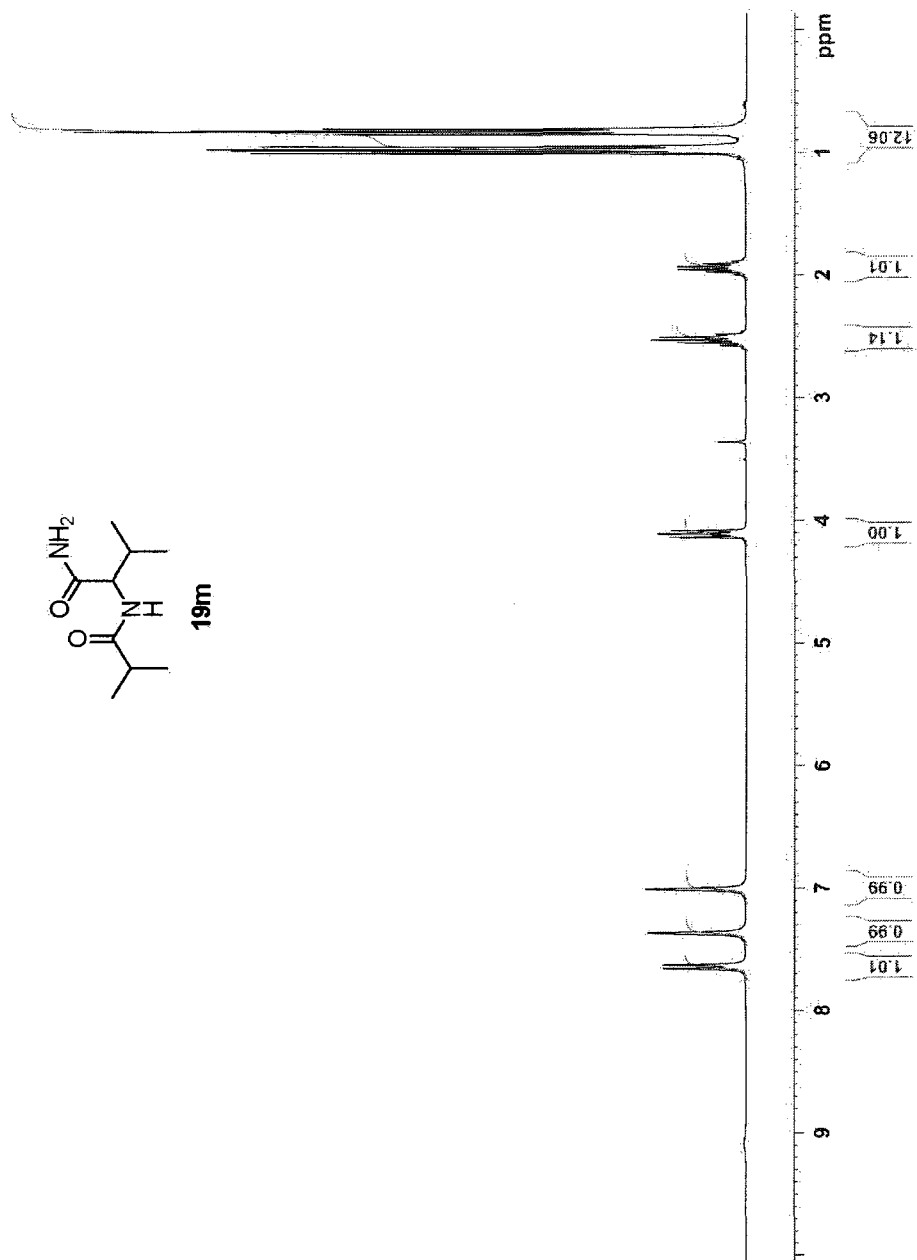


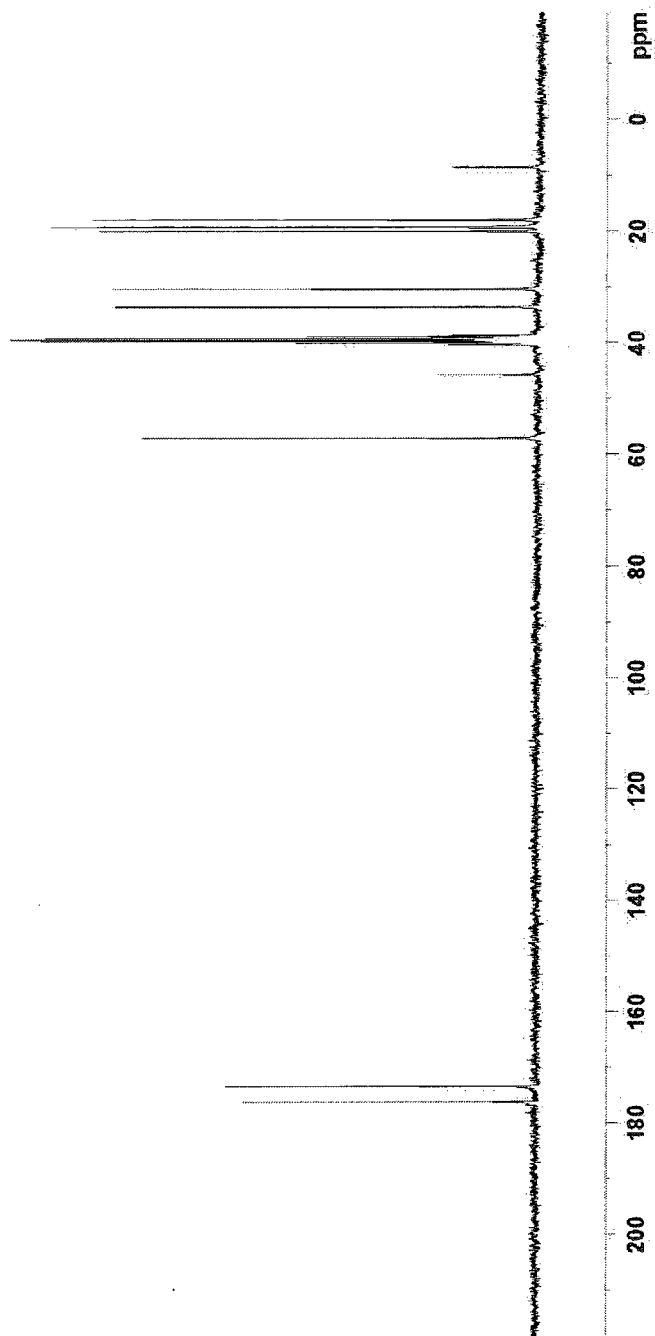
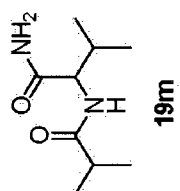


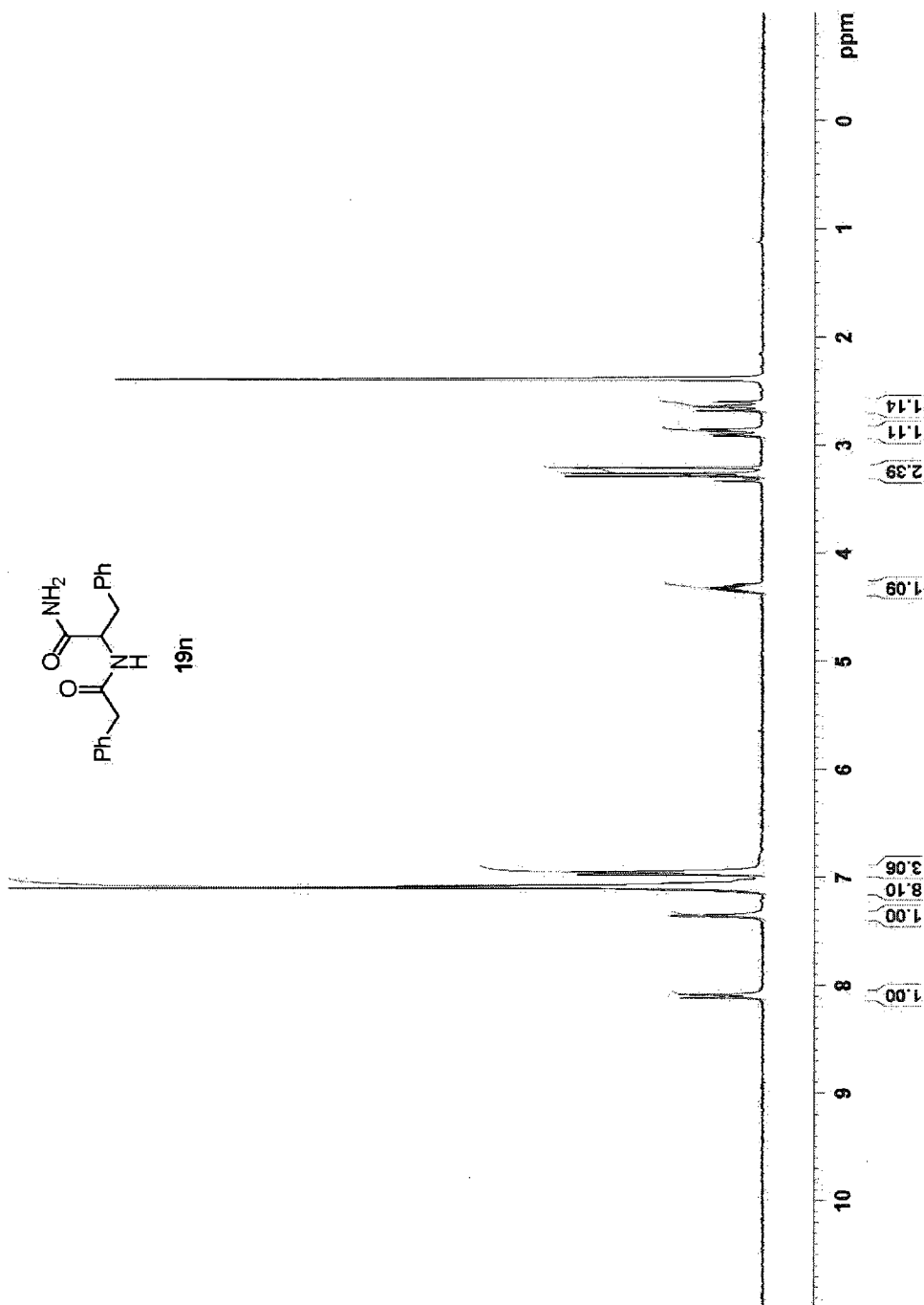


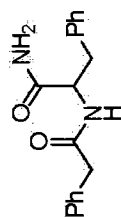




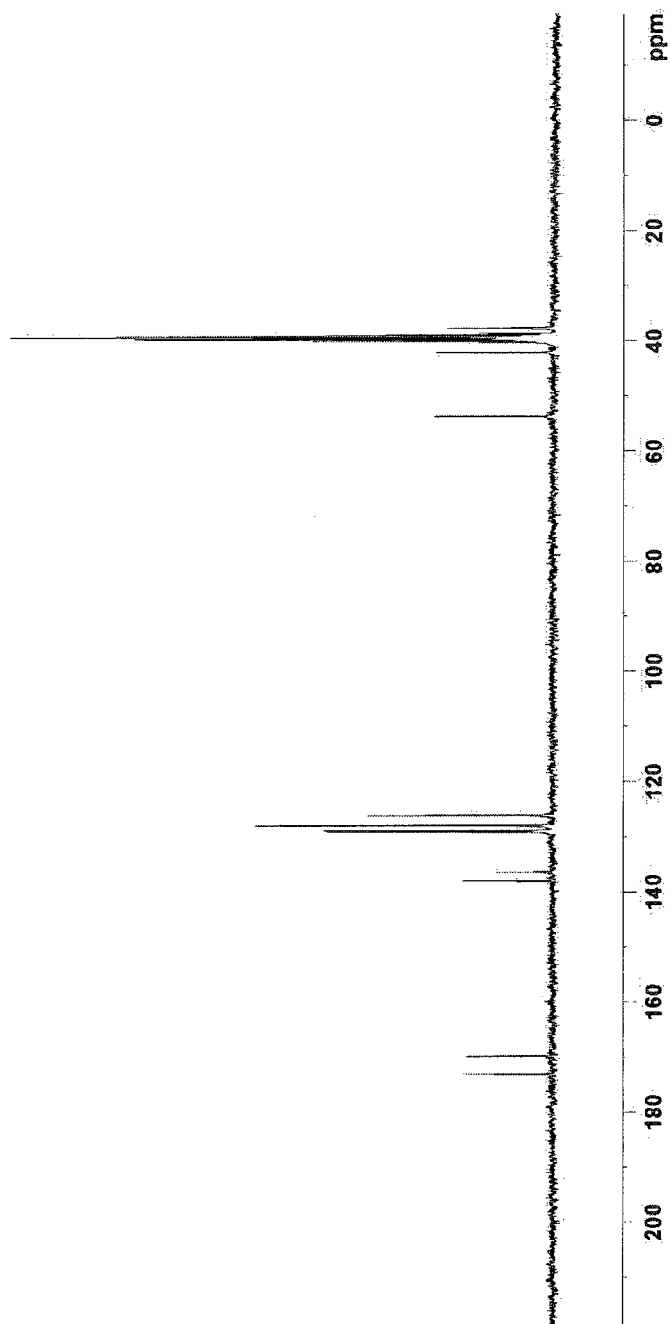


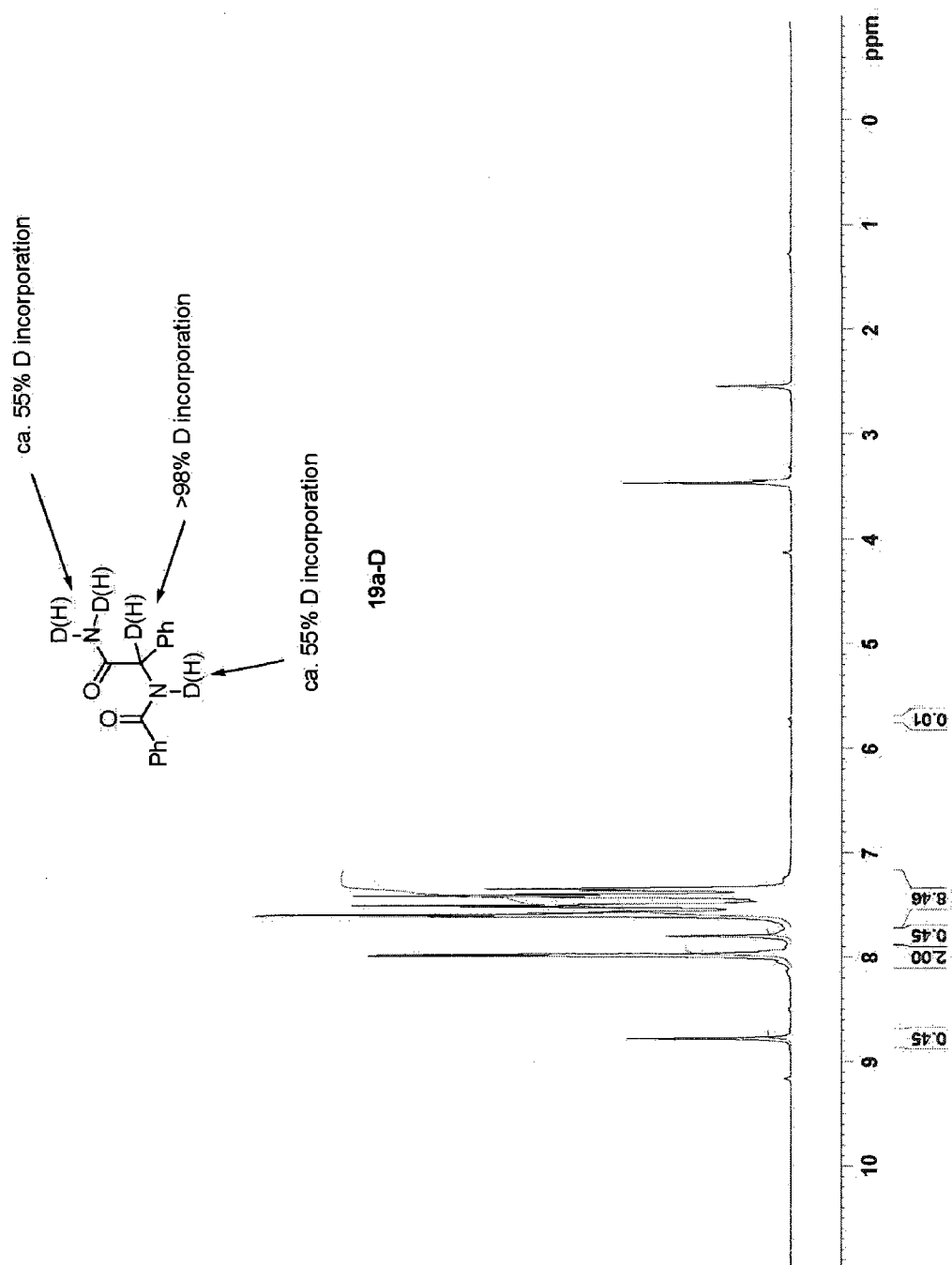


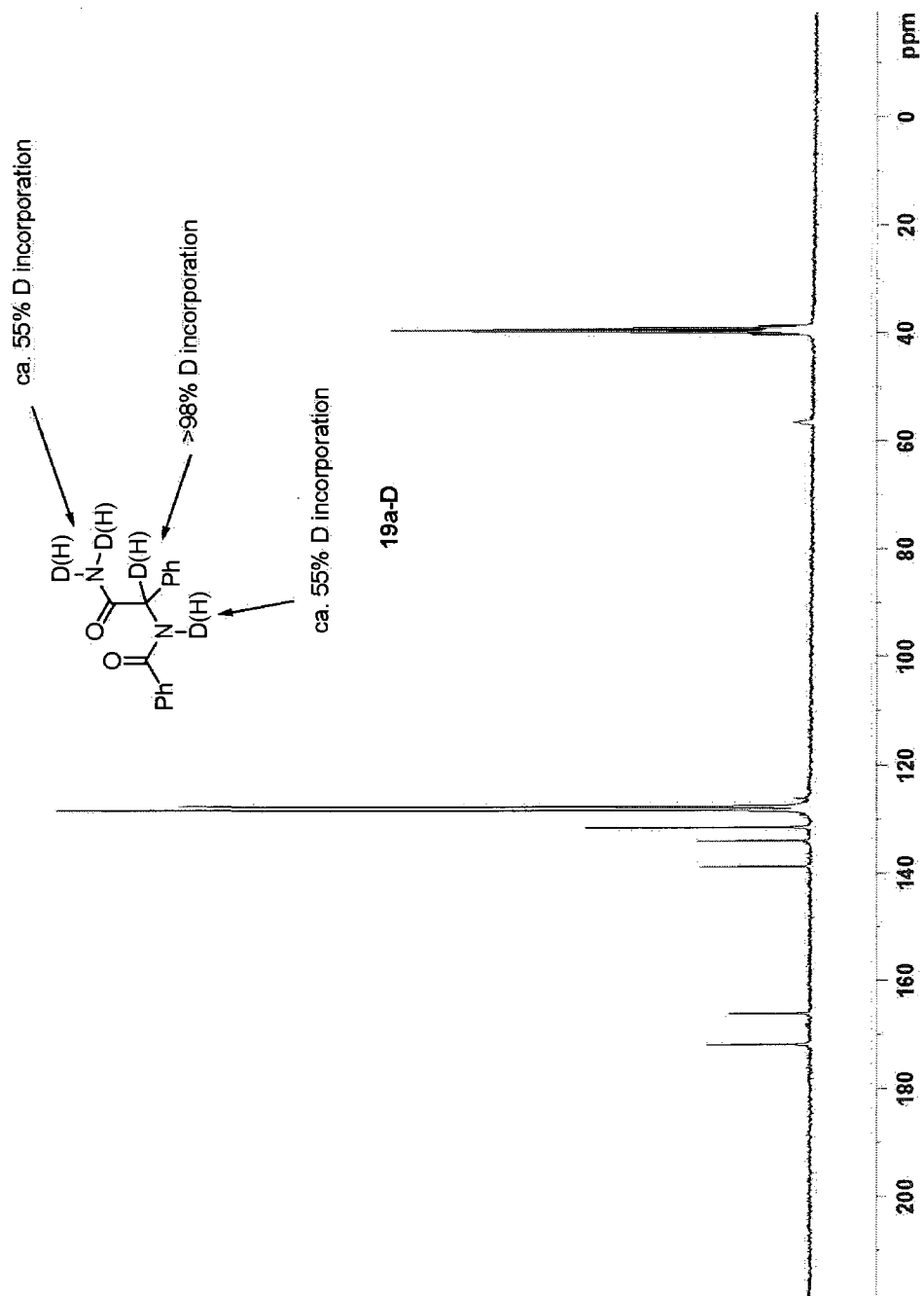


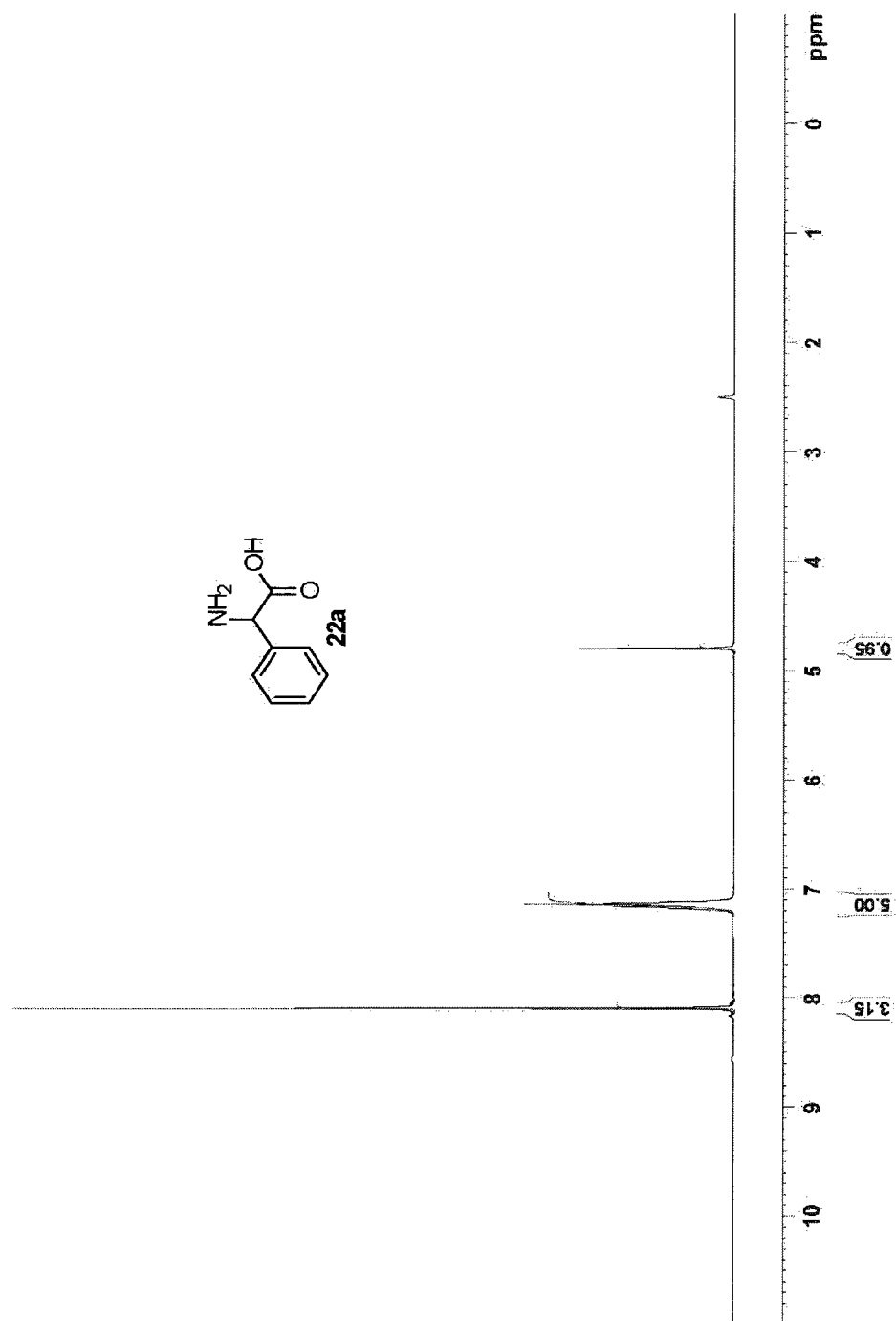


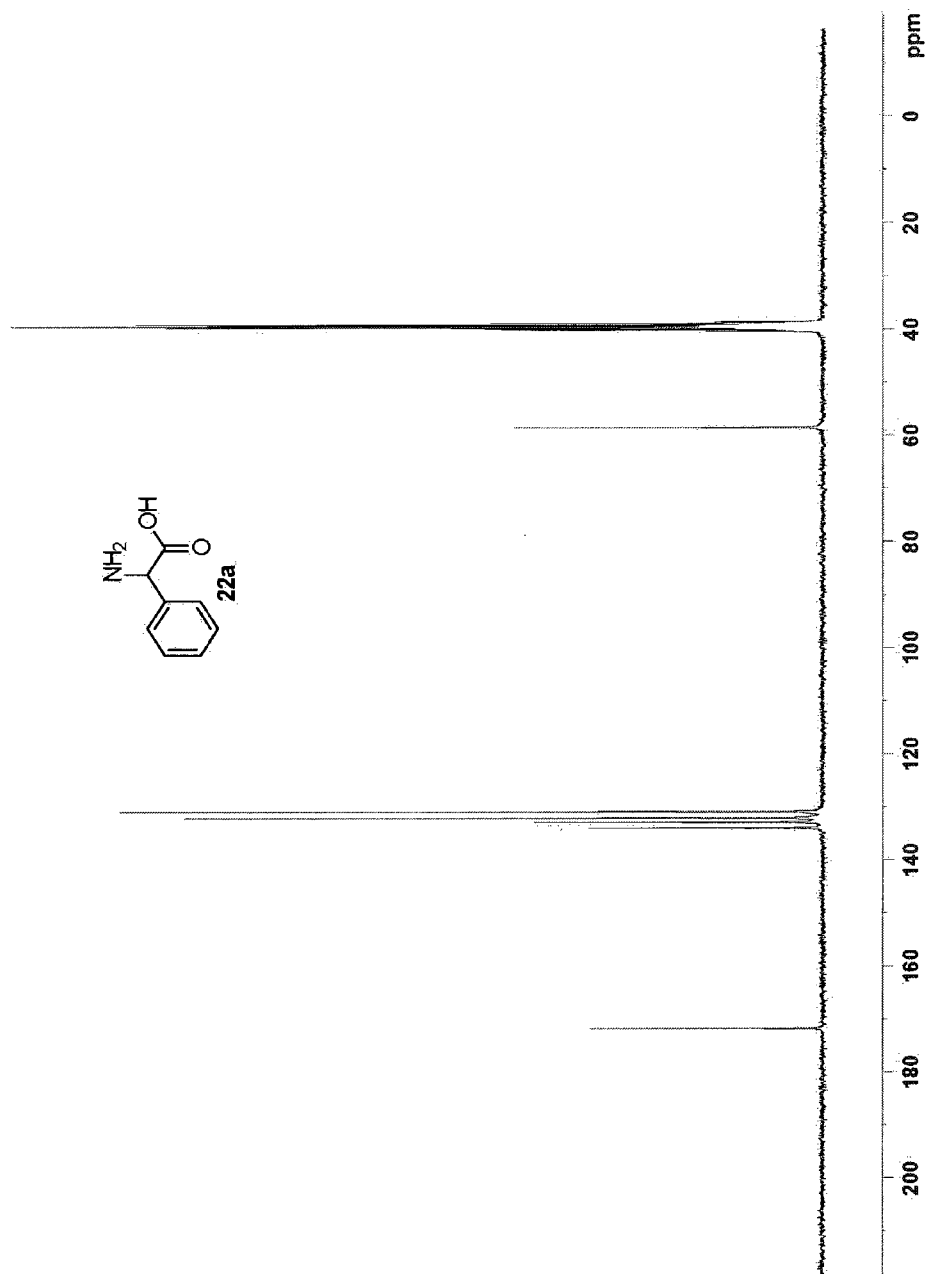
19n











Chapter II:

Synthesis of chiral formamidinium salts as precursors to acyclic diaminocarbenes.^{‡§}

1. Introduction

1.1. Enantioselective catalysis

1.1.1. Catalysis

Catalysts are substances used in substoichiometric amounts to accelerate chemical reactions without being consumed or chemically altered (i.e. they are recycled throughout the process). Catalysts bind substrates to facilitate chemical reactions, and release the products before re-entering the cycle. Catalytic activity consists of lowering the activation energy of reactions by providing an alternative lower-energy pathway (Figure 4). The entire process is therefore concerned with reaction kinetics.⁴¹

The catalyst is not consumed during the process, and it may repeat the cycle as long as the substrate is still present, and as long as it is not decomposed. The number of times the catalyst repeats the catalytic cycle, either before it is consumed or before the reaction is completed, is called the turnover number (TON). The frequency at which the catalyst completes each cycle is called the turnover frequency (TOF).

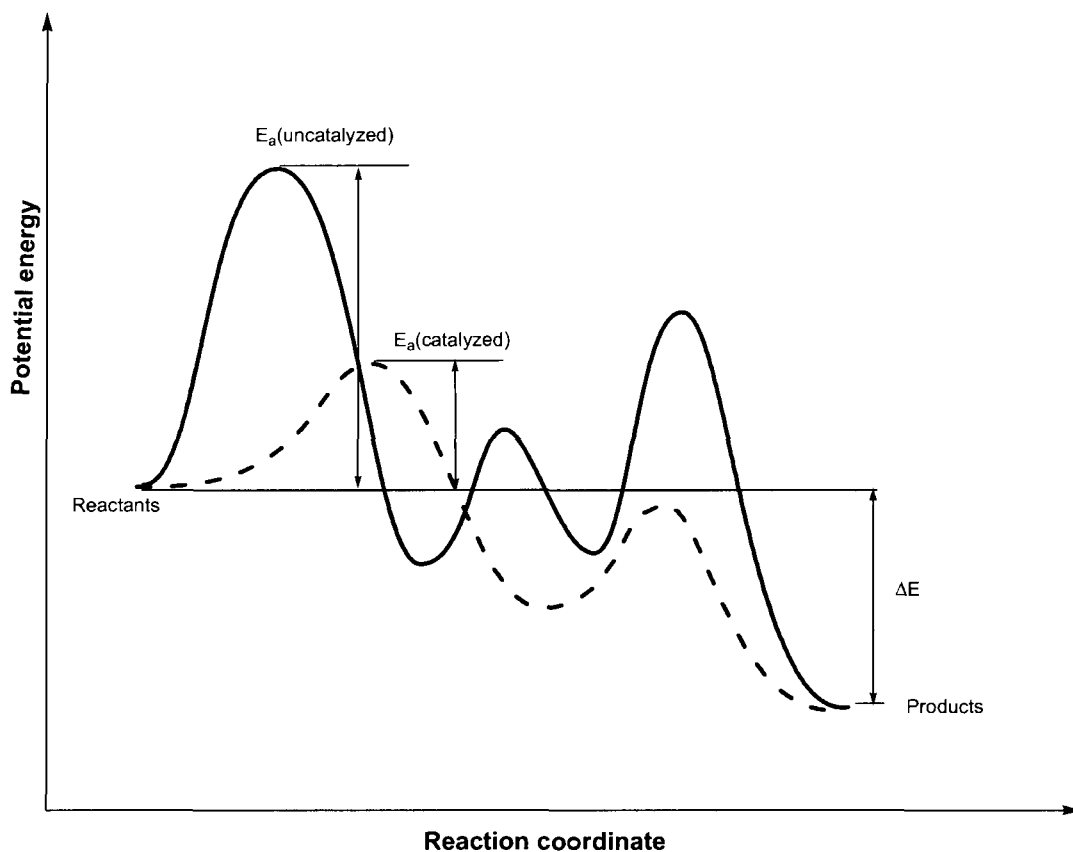
The term homogeneous catalysis is used for reactions in which the catalyst is in the same phase as the reaction mixture. Heterogeneous catalysis occurs when the catalytic

[‡] Mira Beshai collaborated in the synthesis of the formamidinium salts **102-106**.

[§] Ben Cooper and Dr. Charles Macdonald solved the crystal structures of **102-I** and **117**.

reaction is conducted at the interface of two immiscible phases (an example is the hydrogenation on Pd surfaces).

Figure 4: Typical energy diagram for a catalyzed and uncatalyzed reaction



1.1.2. Organometallic complexes in catalysis

Organometallic complexes are used as catalysts in a wide range of organic reactions. The catalytic activities of these complexes are highly affected by both steric and electronic properties of the catalyst.⁴² The selectivity and reactivity of the catalysts can be greatly affected by the nature of ligands coordinated to it. This is why much effort in organometallic catalysis is concentrated to ligand design.

The selectivity displayed by a catalyst can be divided into different categories:

- Chemoselectivity: the functional group selectivity, when there is more than one functional group that can react.
- Regioselectivity: when the reacting molecule has two reactive sites that afford different products.
- Diastereoselectivity: when the starting materials have stereocenters and the products are not related as enantiomers.
- Enantioselectivity: the selective formation of one enantiomer from an achiral compound.

High catalytic activities and selectivities have many encouraging advantages including greater environmental friendliness (due to reduced waste) and lower reaction costs.

1.1.3. Multiplication of chirality

In nature some molecules are chiral (non-superimposable molecules that are mirror images of each other). These molecules interact differently with plane-polarized light. Specifically, enantiomers rotate plane-polarized light by an angle of the same magnitude but in opposite directions.^{43, 44}

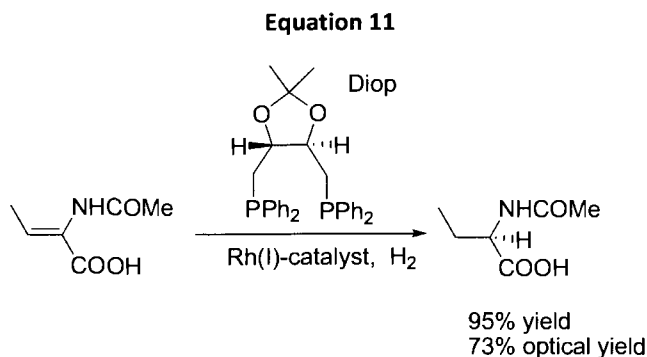
Chirality plays a major role in living organisms where biomolecules, such as enzymes and receptors, interact with chiral compounds with almost perfect specific selectivity. The optical purity of drugs used in pharmaceutical industry is thus of great importance. Different enantiomers of a drug can have different physiological properties, and the opposite enantiomer of a drug can sometimes display adverse physiological properties.⁴⁵ In addition, chiral compounds exhibit certain physical properties that are desirable in highly functional materials such as electronics and optics.⁴⁴

The preferential synthesis of one enantiomeric form over the other is called enantioselective synthesis. The synthesis can be achieved by any of three methods: (i) appending chiral auxiliaries to substrates, (ii) the use of stoichiometric chiral reagents, or (iii) the use of chiral catalysts. In the case of chiral auxiliaries, the synthesis requires additional

steps of appending and removing the stereodirecting auxiliaries. In the case of stoichiometric chiral reagents, the issue becomes the expense of the stoichiometric chiral reagents. On the other hand, with chiral catalysts, the enantioselective synthesis can be achieved catalytically.^{44, 46} Thus with a catalytic amount of chiral complex, a large amount of enantioenriched compound can be generated, whence the term “multiplication of chirality”. However, the design of such catalysts is not straight forward since little is known about the catalytic transition states and intermediates. Nevertheless, it is known that chiral ligands impart chirality to the transition metal catalysts, and if the steric and electronic properties are tuned properly, high enantioselectivity can be achieved. One way to impart chirality on transition metals is the use of chiral ligands, and the two classes that have been of interest to us are those with C_2 -,^{47, 48} and C_1 -symmetry.⁴⁹

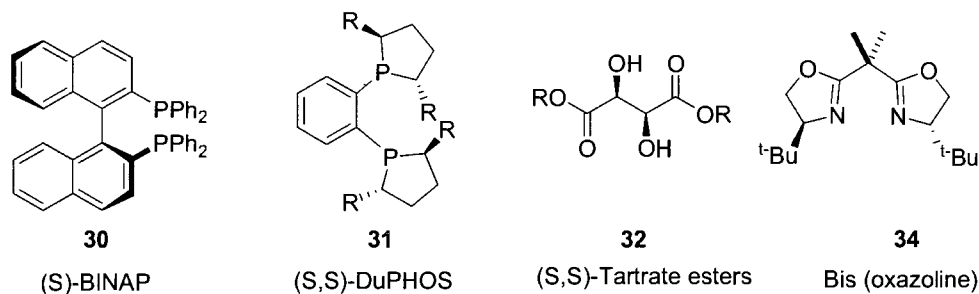
1.1.3.1. C_2 -symmetric ligands

C_2 -symmetric molecules have only a 2-fold rotation axis symmetry operation (simple rotation). They lack the plane of reflection and for this reason they are dissymmetric and chiral.⁵⁰ In asymmetric synthesis, the presence of the C_2 -symmetry axis can serve the very important function of halving the number of possible competing diastereomeric transition states.⁴⁸ This group of ligands in asymmetric catalysis was pioneered by the use of the DIOP ligand [(2,3-O-isopropylidene-2,3-dihydroxy-1,4bis(diphenylphosphino)butane)], which displayed high enantioselectivity for the first time in enantioselective catalysis (Equation 11).⁵¹

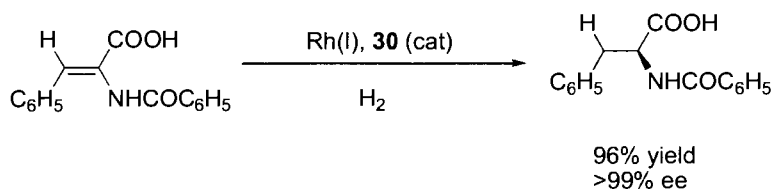


Other C_2 -symmetric ligands have been designed, and many have been found to be useful and effective in enantioselective catalysis. A few of the most successful C_2 -symmetric ligands are shown in Figure 5. BINAP (2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl) **30**, as reported by Noyori *et al.* showed enantioselectivity up to 100% ee in rhodium catalyzed asymmetric hydrogenation with H_2 in synthesis of enantioenriched amino acids (Equation 12).⁵² DuPhos **31** synthesized by Burk *et al.* in 1991 also showed high enantioselectivity in Rh catalyzed hydrogenation (Equation 13).⁵³ These ligands are classified as “privileged chiral scaffolds” and many other successful ligands have been synthesized by modifying these scaffolds.⁴⁷

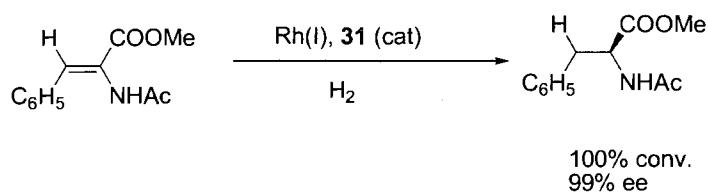
Figure 5



Equation 12



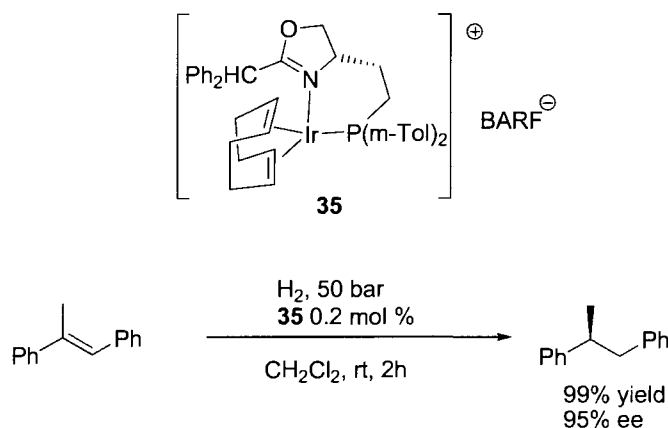
Equation 13



1.1.3.2. C₁-symmetric ligands

Although C₂-symmetry has been thought to be the central guiding principle in ligand design for asymmetric catalysis, it is not a necessary condition for achieving high enantioselectivity. In fact, recently, Pavlov *et al.* have done a systematic comparison of C₂-symmetric and C₁-symmetric ligands. In many cases C₁-symmetric ligands provide higher enantioselectivities than the corresponding C₂-symmetric variants. The superiority of C₁-symmetric ligands is also displayed in nature where stereo-specific processes are accomplished in living organisms with C₁-symmetric molecules such as amino acids, and monosaccharides.⁴⁹ In agreement with many findings in enantioselective catalysis, Pavlov showed that the only legitimate requirement is a catalyst that has a chiral environment close to the catalytic center. A few examples are highlighted below wherein the C₁-symmetric ligands have shown high levels of enantioselectivity.

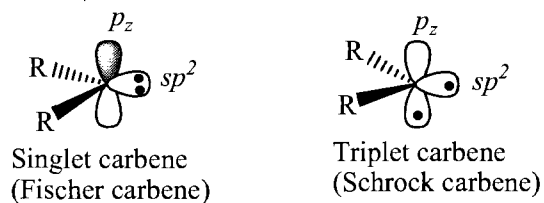
Equation 14



Burgess and coworkers revealed that the complex **35** with chiral phosphine-oxazoline ligands afford high yields and enantioselectivities in the Iridium catalyzed hydrogenation of aryl-alkenes (Equation 14).⁵⁴ It was noticed that the substituted oxazoline unit has a profound effect on both the yield and enantioselectivity, and that Ar₂CH group on the oxazoline unit gave best results. The phosphine substituents were also found to be crucial in enantioselectivity but did not have any noticeable effect on the isolated yields of the

Free carbenes are reactive organic molecules with a divalent carbon with two unshared electrons, which can occupy nonbonding orbitals in two different ways. The carbene carbon is sp^2 hybridized and has two spin states: singlet ($\uparrow\downarrow$) or triplet ($\uparrow\uparrow$). In the singlet state, the two electrons are paired up in the sp^2 orbital, but in the case of triplet state, one electron goes in the sp^2 orbital and the other in the p orbital (Figure 6). This electronic difference accounts for the structural difference, and the resulting chemistry of these carbenes.^{57, 58}

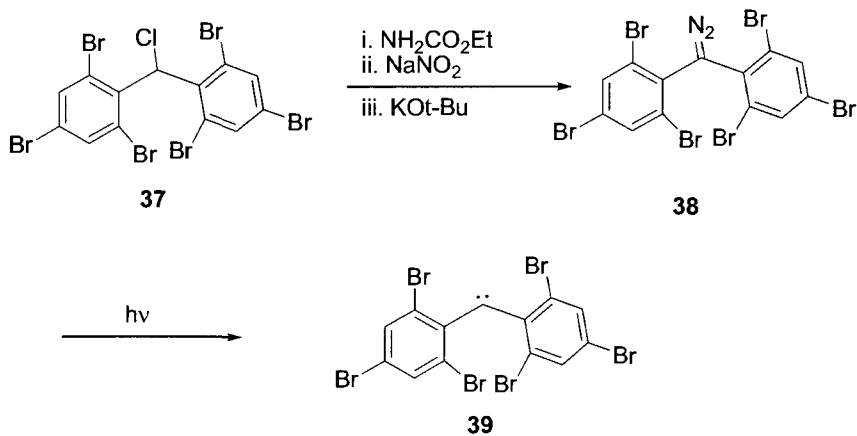
Figure 6



1.2.1. Schrock carbenes and reactivities

Triplet electrophilic carbenes, also known as Schrock carbenes (alkylidenes), bind to higher oxidation state, early transition metals, having non- π -acceptor ligands on the transition metal and non π -donor R groups on the carbene carbon.⁵⁹ The alkylidene transition metals complexes are nucleophilic at the carbenic carbon, and their reactivity is similar to P or As ylides.⁶⁰ They react with Lewis acids such as AlMe_3 , and ketones in the same manner as Wittig reagents. They also react with alkenes to form metalacycles, which may decompose in various ways.⁶¹ One of the decomposition pathways leads to olefin metathesis, a very useful reaction in organic synthesis.^{62, 63}

Scheme 6



Although triplet carbenes are highly reactive, shielding the carbenic center can substantially expand their life time. Thus, Tomioka and coworkers were able to synthesize and isolate the first free triplet carbene **39** with bulky aromatic groups attached to the carbenic carbon (Scheme 6).⁶⁴ Although crystals of **39** were found to be stable enough even under aerobic conditions, the thermodynamic stability of these carbenes is nevertheless very limited.

1.2.2. Fischer carbenes and reactivities

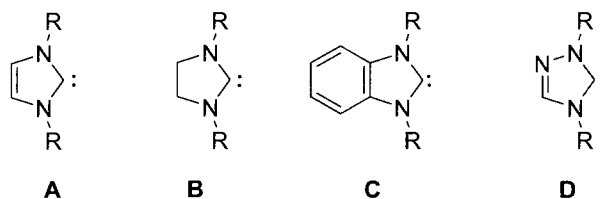
The singlet carbenes, also known as Fischer carbenes, are nucleophilic. Heteroatom groups (O, N, S) bonded to the carbenic center, enhance the nucleophilicity through π -donation,⁵⁹ and make the otherwise degenerate singlet orbitals unequal in energy.⁵⁷ The singlet carbenes bind to low oxidation state, late transition metals, having non- π -acceptor ligands. Fischer carbenes are two electron σ -donors via the carbene lone pair, but the empty p orbital on carbon is also a weak acceptor for π back donation from the metal d_{π} orbitals. This makes the carbene carbon electrophilic because the σ -donation to metal is not fully compensated by π -back donation. For this reason, Fischer carbene complexes are susceptible to nucleophilic attack at the carbenic carbon. In most cases, the bond between the carbenic carbon and the heteroatom is shorter than a single bond, further proving the double bond character due to the π -donation from the heteroatom. The metal-carbon bond (M-C) has also a bond order greater than one, due to the contributing metal to ligand π -back bonding.

1.2.3. Diaminocarbenes

1.2.3.1. N-heterocyclic carbenes (NHCs)

NHCs are heterocyclic carbenes with at least one nitrogen atom adjacent to the carbene. The most commonly encountered NHCs are imidazolylidene **A**, imidazolinylidene **B**, benzimidazolylidene **C** and triazolylidene **D** (Figure 7). A considerably large number of such derivatives have been synthesized and studied in many areas of chemistry.⁶⁵

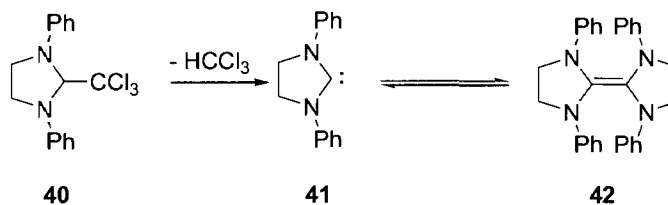
Figure 7



Historical breakthroughs

In early 1960s Wanzlick and coworkers demonstrated that by increasing the π -donating ability of triplet carbene substituents, the nucleophilicity of the carbene is increased.⁵⁹ Distinct nucleophilicity was observed in the case of diaminocarbene **41**. The isolation of the free diaminocarbenes however could not be achieved because they were found to undergo a reversible dimerization upon formation (Equation 16),^{66, 67} and also to react with a wide range of electrophiles including water, oxygen, nitromethane, acids, aldehydes and ketones (Scheme 7). The same nucleophilic reactivity was observed when the isolated NHC dimer was reacted with the electrophiles, which further supports the equilibrium process between the free NHC **41** and its corresponding dimer **42** (Equation 16).

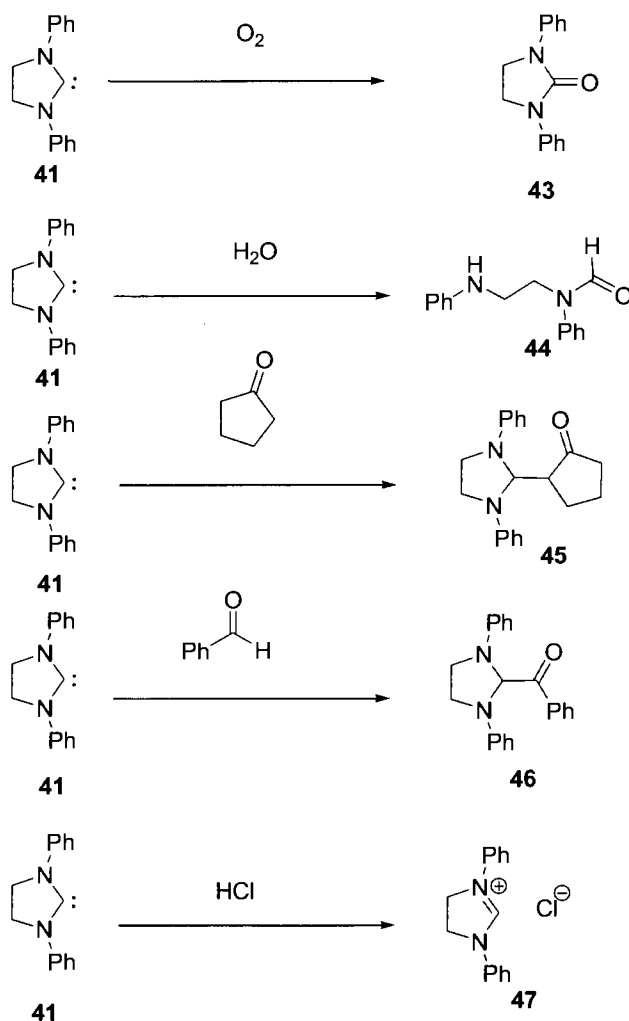
Equation 16



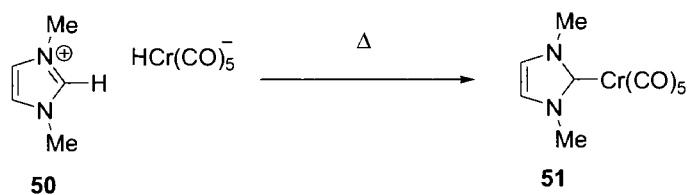
The treatment of carbene **41** with mercury acetate by Wanzlick *et al.* gave a bis-carbene mercury complex (Equation 18).⁶⁸ The acetate ligand deprotonates the imidazolium salt to give acetic acid and the free carbene which then coordinates to the transition metal *in situ*. In the same year, Öfele *et al.* reported the synthesis of the chromium complex (Equation 17). These two methods, used by both Wanzlick and Öfele to synthesize the transition metal carbene complexes, avoid the isolation and handling of reactive free carbenes.

In early 1990s, Arduengo and coworkers reported the successful isolation of the first free NHC **53** (Equation 19).⁶⁹ This discovery opened up a whole new field in organometallic chemistry. More insight into their properties was gained, and their application and utility were better understood and extensively exploited, especially in the area of transition metal catalysis.^{65, 70, 71} The resonance stabilization in unsaturated heterocyclic backbone of **53** was suggested as a requirement to isolate the carbenes. The necessity of aromaticity was however experimentally refuted through the isolation of imidazolin-2-ylidenes by Arduengo *et al.*⁷² and Denk *et al.*⁷³ as well as the isolation of acyclic diaminocarbene by Alder *et al.*⁷⁴

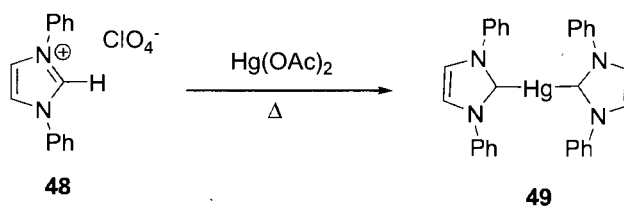
Scheme 7



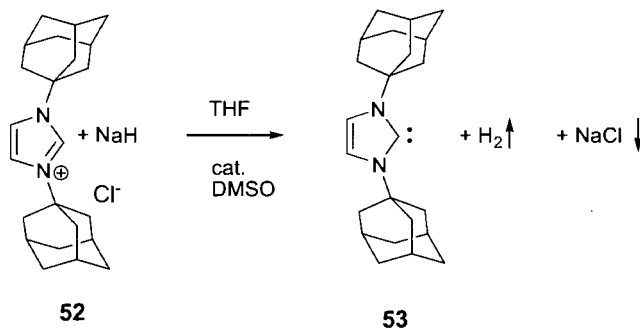
Equation 17



Equation 18



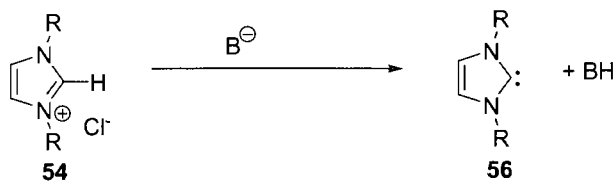
Equation 19



General synthesis of NHCs

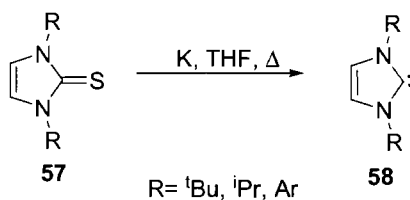
NHCs are generally synthesized by deprotonation of the corresponding imidazolium and imidazolinium salts with a base such as NaH , LDA , KO^tBu (Equation 20).⁷⁵⁻⁷⁷

Equation 20



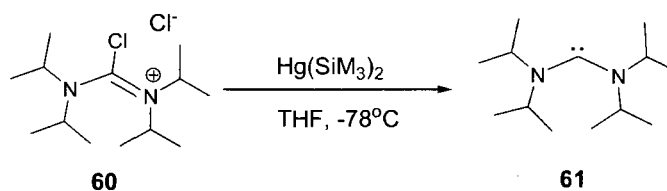
The desulfurization of thiourea derivatives with potassium has also been reported. This method is usually preferred over the previous methods for sensitive substrates (Equation 21).^{73, 78}

Equation 21



In addition, chloroamidinium salts (60) react with $Hg(SiMe_3)_2$ to furnish the corresponding diaminocarbene (61), with less side reactions observed than when alkali metals were used (Equation 22).⁷⁹ This method is also quite efficient due to the mild conditions used.

Equation 22

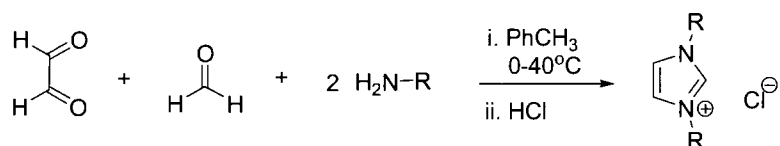


Synthesis of azolium salts

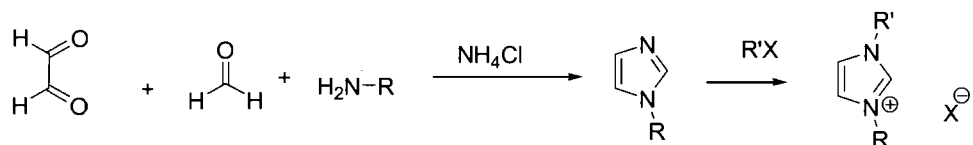
The method most often used for the synthesis of NHCs is through the deprotonation of the corresponding azolium salts (Equation 20). The popularity of this route is due to the facile access to the azolium precursors from easily accessible starting materials. The

symmetrically substituted imidazolium salts are typically synthesized through a one pot three component reaction of formaldehyde, glyoxal and two equivalents of the appropriate primary amines (Equation 23).^{75, 80} The dissymmetrically substituted imidazolium salts are synthesized in the same manner but with one equivalent of the primary amines to give N-monosubstituted imidazoles which can then be subsequently alkylated with other electrophiles (Equation 24).⁶⁵ The imidazolium salts can also be synthesized via a stepwise alkylation of imidazole.⁸¹

Equation 23

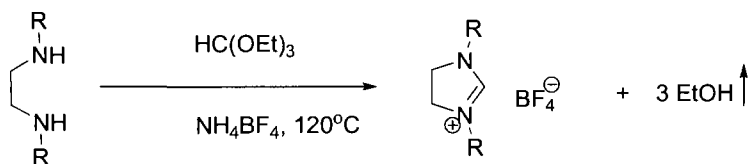


Equation 24



Imidazolinium salts are efficiently synthesized by reacting ortoformate with 1,2-ethyl-diamine derivatives (Equation 25).⁸² This methodology is very flexible because the substitution on the heterocyclic backbone can be purposely varied by changing the substitution pattern of the starting diamine.

Equation 25

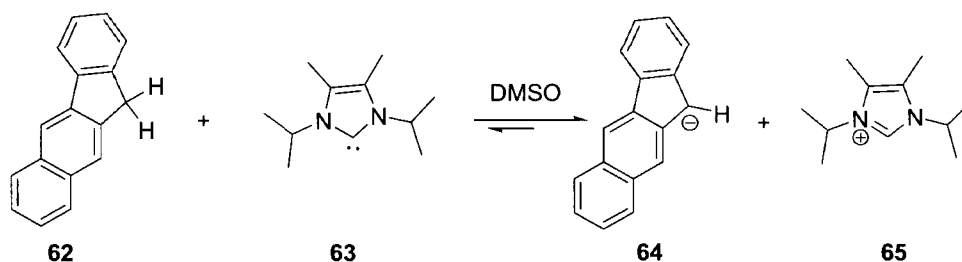


Electronic and steric stabilization of NHCs

The thermodynamic stability of free NHCs is mainly due to the stabilization of the sextet carbon by the adjacent nitrogen atoms through a π -donation to the empty p -orbital

and an accompanying σ -withdrawal, i.e. a push-pull phenomenon.^{83, 84} The degenerate singlet orbitals are then rendered unequal in energy, leading to the spin-pairing of electrons and thus increasing the nucleophilicity and electron richness at the carbenic center. Free NHCs have an increased energy gap between the HOMO and the LUMO. The increased energy gap contributes to their increased thermodynamic stability over other singlet carbenes.⁸⁵ The Lewis basicity of NHCs are very broad. They forming complexes with almost all metals (transition metals discussed in more details in the next section), as well as weak Lewis acid such as iodopentafluorobenzene,⁸⁶ and iodide.⁸⁷ A proton complex has also been reported.⁸⁸ NHCs are also Brønsted bases with pKa values well above 23.5 in deuterated DMSO, which makes the NHCs among the strongest neutral bases.⁸⁹ The basicity was assessed via the deprotonation of a number of acidic compound, such as fluorene (pKa 22.9 in DMSO), 2,3-dibenzofluorene **62** (pKa 23.5 in DMSO) which were both completely deprotonated by 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene **63** (Equation 26).

Equation 26



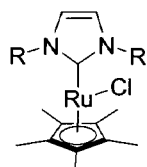
In addition to electronic features, the steric bulkiness of the N-substituents contributes to the kinetic stabilization of NHCs by shielding the carbene center.⁹⁰⁻⁹²

NHC-transition metal complexes and catalysts

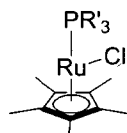
NHC complexes are generally synthesized by ligand substitutions at the metal center. Either isolated NHCs or *in situ* generated NHCs are used to form stable NHC-metal complexes, with very robust metal-NHC bonds. Transmetalation with Ag-NHC complexes is among the most efficient routes to synthesize other metal complexes for two reasons: (i) the

Ag-NHC complexes are easily synthesized from azolium salts and silver oxide, (ii) the transmetallation avoids the handling of reactive free NHCs. Transition metals with associated basic ligands (e.g. acetate-metal complexes) that can deprotonate the azolium salts *in situ* can also be used. This is the same method Wanzlick used in the synthesis of the bis-NHC mercury complex (Equation 18).⁶⁸

NHCs, as ligands of transition metals, are two electron donors with little to no π -back-donation.⁹³⁻⁹⁶ Due to the π -donation from the two nitrogen atoms, little or no π -donation from the transition metal center is required for stability. This electronic feature leads to the formation of robust metal-NHC bonds, which are quite often referred to as inert.⁹² Some cases, however, have been reported where NHCs dissociate from the metal.⁹⁷⁻¹⁰² The metal-NHC bond dissociation energies (BDE) are affected by steric bulkiness of the NHC substituents.^{91, 92} Increased bulkiness leads to less orbital interaction which is observed in lengthened metal-NHC bonds and thus weaker bonds. Nevertheless, the weakest metal NHC bonds are much stronger than the strongest metal-phosphine bonds. For example, in the ruthenium complex of 1,3-dimesitylimidazolylidene, **66b** was found to have a BDE of 15.6 kcal/mol whereas the corresponding phosphines **67a** and **67b** complexes have 9.4 and 10 kcal/mol, respectively. The bulkier 1,3-diadamantylimidazolylidene **66a** on the other hand has a relative BDE of 6.8 kcal/mol, which is not surprising considering the steric hindrance of the bulky adamantyl groups.⁹¹



66a R: adamantyl
66b R: mesityl

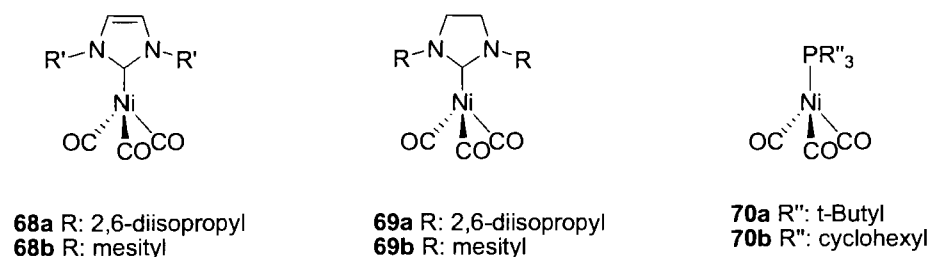


67a R': isopropyl
67b R': cyclohexyl

The difference in the electron donating ability between NHCs and phosphines has been evaluated from CO stretching frequencies of their carbonyl complexes IR spectra. The premise of evaluating the CO stretching frequencies is as follows: the stronger σ -donating ligands increase the electron density at the transition metal, which in turn is donated to

carbonyl ligands through π -back bonding. As this electron density is pushed into the π^* orbitals of CO, the bond order of CO is reduced and CO stretching frequency is lowered. The Tolman electronic parameters (TEP), one of the methods to compare ligands' electronic properties, is based on the $\nu(\text{CO})$ stretching frequencies in their $\text{Ni}(\text{CO})_3$ complexes. The CO stretching frequencies range between 2052.2 cm^{-1} and 2050.7 for complexes **68** and **69**, whereas the frequencies in **70a** and **70b** are 2056.1 and 2056.4 cm^{-1} , respectively. NHCs are thus better electron donating ligands than even the electron rich trialkyl phosphines.^{103, 104} The enhanced electron donating ability is thus an advantage in catalysis where an electron rich metal center is required. For example, the oxidative addition of otherwise resilient organochloride species to palladium catalyst has been achieved due to coordination of NHC ligands. The oxidative addition step is an important step in catalytic cycle coupling reactions.

Figure 8

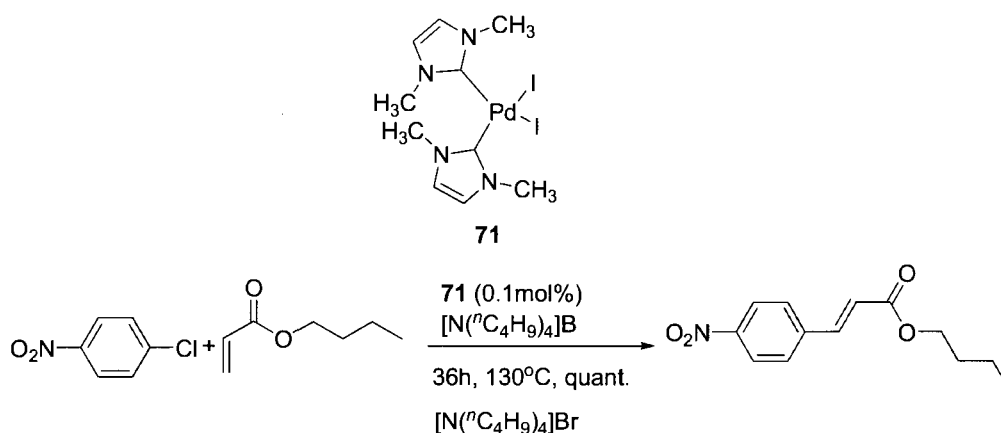


Another advantage that NHCs have over phosphines is that the NHC-metal complexes are far more stable than phosphine metal complexes. Several NHC-metal complexes resist harsh conditions such as air and high temperatures in solvents, and can be isolated through silica gel column chromatography.¹⁰⁵ The enhanced stability of these complexes is useful in transition metal catalysis because higher turnover numbers can be achieved and lower catalyst loadings can thus be used (due to reduced catalyst decomposition).

The first reported use of NHC-metal complexes in transition metal catalysis appeared in 1995 by Herrmann *et al.* (Equation 27).¹⁰⁵ A nearly quantitative Heck cross-coupling reaction was conducted at $130\text{ }^{\circ}\text{C}$ for 36 hours with 0.1 mol% loading of catalyst **71**. The catalyst **71** melts at $299\text{ }^{\circ}\text{C}$ without decomposition, and resists several days' treatment with oxygen in

boiling THF. Herrmann concluded this report as follow: "The new catalyst type described here has a series of advantageous properties and potential for development: a) high thermal and hydrolytic durability resulting from exceptionally stable M-C bonds (long shelf-life, stability to oxidation), b) easy accessibility, and c) no need for an excess of the ligand. The prospects for derivatization to water-soluble catalysts (two-phase catalysis), immobilization, and chiral modification seem promising because of the constitution of the ligands."¹⁰⁵

Equation 27



Ever since this first report by Herrmann, NHCs have become common ligands in transition metal catalysis.^{65, 70}

Chiral monodentate NHCs in enantioselective catalysis

Enantioselective catalysis using chiral NHCs was pioneered by Herrmann and coworkers in 1996.¹⁰⁶ This research area did not meet with great success at first, but through extensive modification, some NHCs have shown high levels of enantioselectivities in a few select reactions.

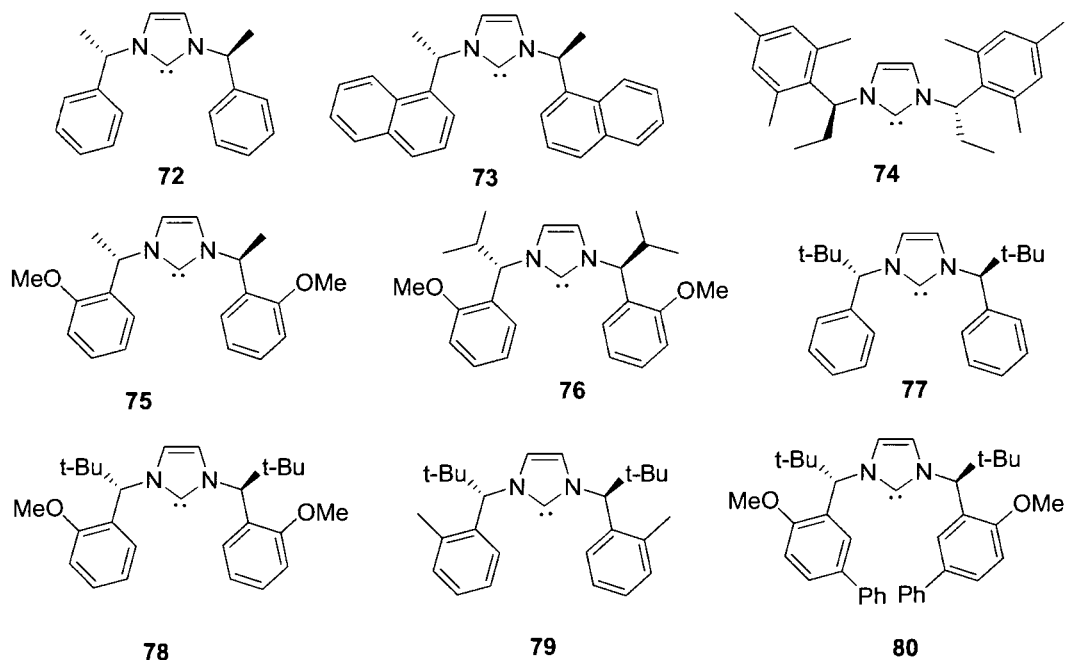
Next a brief review of the accomplishments in this area of research is presented with a focus on the key factors that are known to be important for high activities and enantioselectivities.

- **Symmetrically substituted monodentate NHCs (C_2 -symmetric)**

Imidazole based chiral NHCs

Chiral NHCs with an imidazole backbone that have been studied thus far bear the chirality within the N-substituents. While **72** and **73** were the first to be reported, only limited enantioselectivities were obtained with these ligands by Herrmann and coworkers. In the Rh(I) catalyzed asymmetric hydrosilylation, good to excellent yields were obtained as expected with TON up to 900, but the highest enantioselectivity observed was 32% ee with **73**-Rh(COD)Cl precatalyst (Equation 28).¹⁰⁶

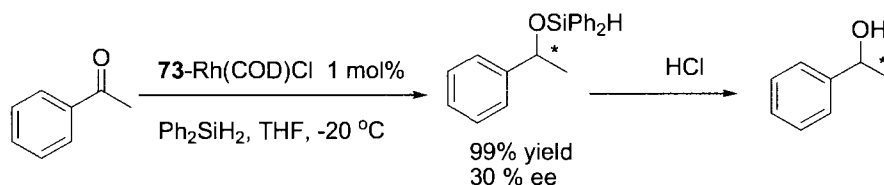
Figure 9: Select examples of chiral NHCs ligands with an imidazole back bone



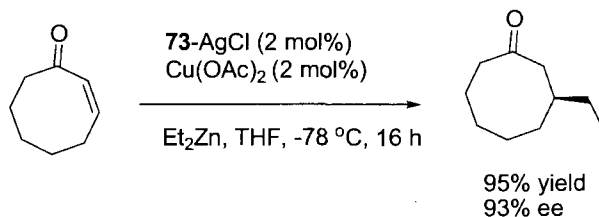
Unsatisfactory enantioselectivities were also obtained in the asymmetric copper catalyzed 1,4-conjugate addition of organozinc reagents to enones.¹⁰⁷ Enhanced enantioselectivities in the Cu-catalyzed 1,4-conjugate addition of diethyl zinc to cycloheptenone were only obtained with **73**-AgCl/Cu(OAc)₂ pre-catalyst system (Equation 29).^{81, 107} The silver-carbene complex as source of NHC was found to be the more

preferential route to generate the copper-NHC *in situ*. The advantage of this method is that it avoids the use of bases, which can lead to the loss of chirality in the ligand. The increase of steric bulkiness of the nitrogen substituents of **73** lead to decreased activities and no improvement of selectivity. Despite these improved reaction conditions, however, the enantioselectivity remained low for a range of substrates.

Equation 28

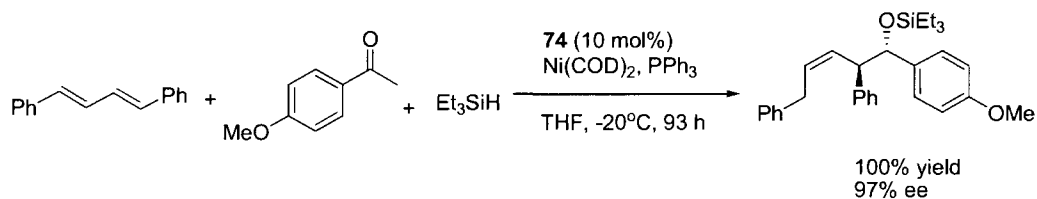


Equation 29

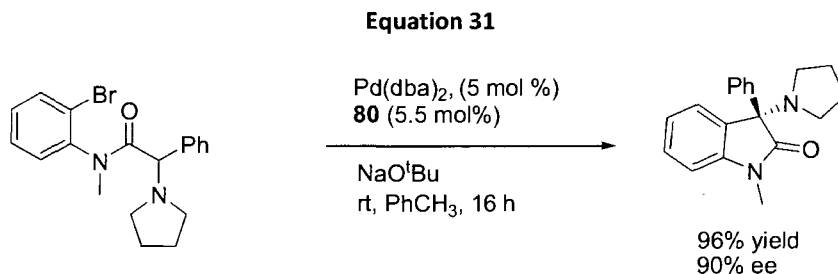


In the Ni catalyzed three-Component coupling of 1,3-Dienes, aldehydes, and silanes, it was observed that the bulkiness of the N-substituents of the NHCs is of great importance (Equation 30).¹⁰⁸ The NHC **74** was more selective than **73**, which was in turn more selective than **72**. The enantioselectivity was also high for the more steric demanding dienes.

Equation 30



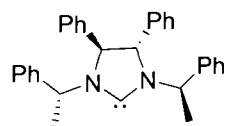
Kundig *et al.* have studied the steric and substitution effect in NHCs **75-80** in the Pd-catalyzed asymmetric α -arylation of amides.^{109, 110} The benzylic t-butyl group in **78-79** was found to be much more selective than the less bulky substituents. While the methoxy group in **78** was found to be crucial, the highest yields and enantioselectivities were obtained with **80**, although the rationalization of these findings has yet to be addressed.¹⁰⁹



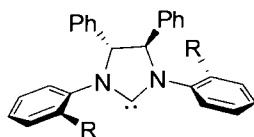
Imidazoline based chiral NHCs

In addition to the ability of placing the chirality within the N-substituents, NHCs with imidazoline backbone can also have chirality within the heterocycle. It has been argued that the chirality within the heterocycle can restrict the inherent rotation in N-substituents and thus enforce the pre-existing chirality of the ligands.¹¹¹ For example, the use of **90** in asymmetric ring closing metathesis of an achiral triene resulted in very good enantioselectivity (Equation 32).¹¹¹

In addition Tomioka and coworkers have revealed that Cu-**82** complexes display high efficiency and enantioselectivity in the asymmetric conjugate addition of Grignard reagents to cyclohexenone derivatives (Equation 33).¹¹² The N-aryl disposition close to the catalytic center is believed to be the source of high enantioselectivities. N-alkyl substituents (such as **81**) however fold away from the metal center making the chirality of the catalytic center less well defined.

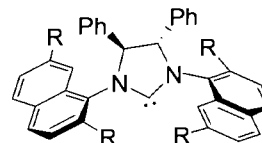


81



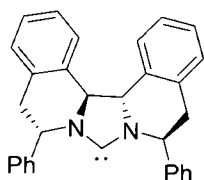
82

a: R= iPr
b: R= OMe
c: R=Me

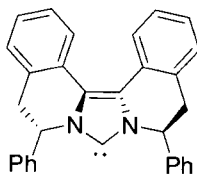


83

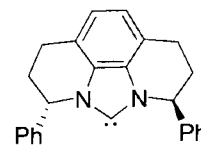
R = i-Pr



84

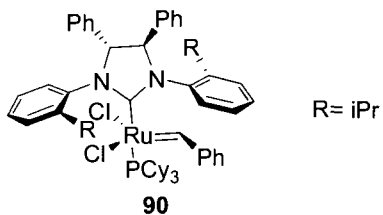


85

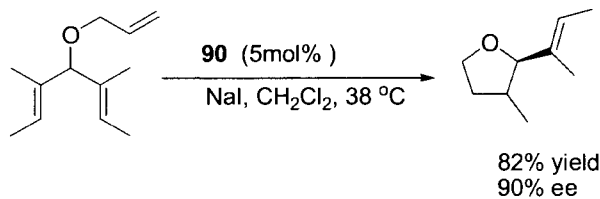


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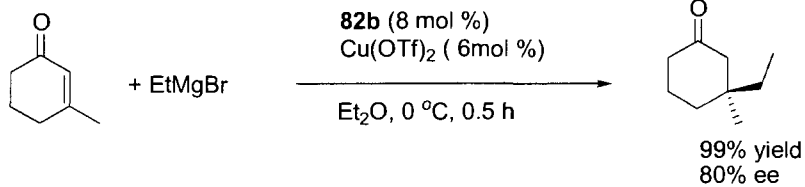
Equation 32



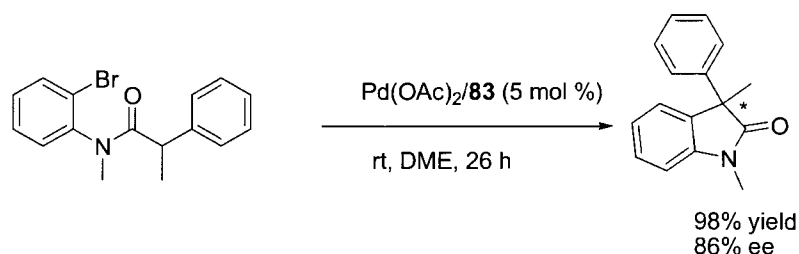
90



Equation 33

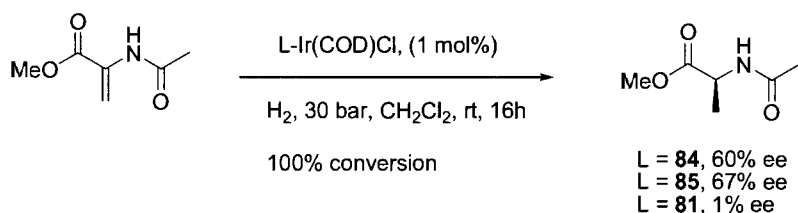


Equation 34



Herrmann *et al.* recently reported the synthesis of rigid NHCs **84** and **85** which afforded moderate levels of enantioselectivities in iridium catalyzed enantioselective hydrogenation of alkenes (60% to 67% ee).¹¹³ The limited flexibility of these ligands is believed to be the source of high selectivity (eg. the flexible NHC **81** only afforded 1% ee).

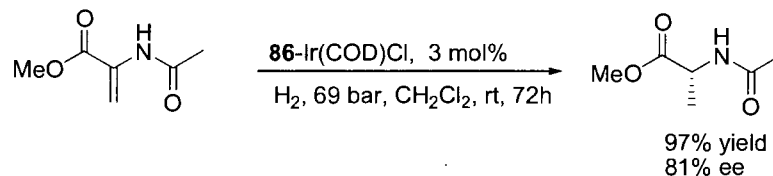
Equation 35



Benzimidazole based chiral NHC

Metallinos also reported the use of the rigid benzimidazolyliidene **86** in iridium catalyzed asymmetric hydrogenation of alkenes as shown in Equation 36.¹¹⁴

Equation 36

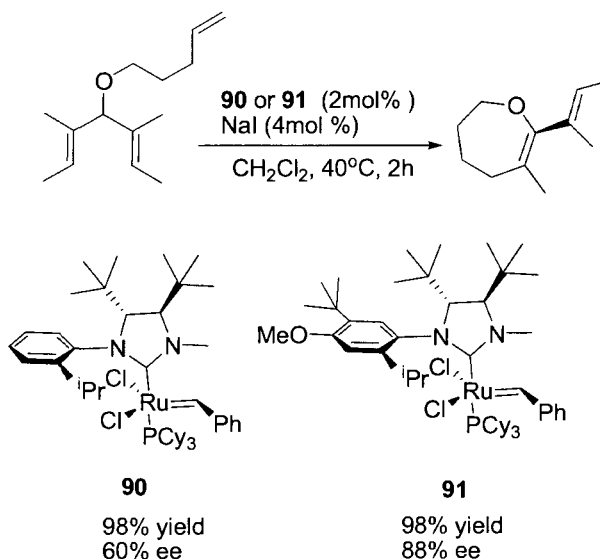


- **Non-symmetrical monodentate NHCs (C₁-symmetric)**

Collins and coworkers recently showed that knowledge of the catalytic mechanism can help a great deal in designing ligands with both high reactivity and enantioselectivity.¹¹⁵

With a C_1 -symmetric NHC ligand, the authors were able to synthesize a ruthenium catalyst for enantioselective ring closing metathesis which displayed high yields and high enantioselectivity in the formation of 5, 6, and 7 membered rings. The two catalysts **90** and **91** have similar reactivities. However, due to steric differences, the catalyst with the bulkier substituents on the aromatic ring (**91**) gave higher enantioselectivities due to the fact that the rotation of the Ru-NHC bond is sterically restricted (Equation 37).¹¹⁵ These C_1 -symmetric ligands were also found to provide better selectivities than the symmetrically substituted variants.

Equation 37

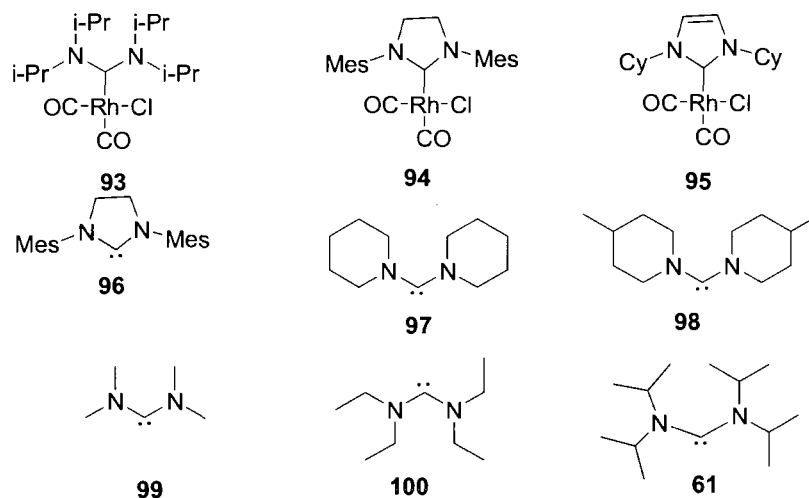


1.2.3.2. Acyclic diaminocarbenes

In 1996, Alder *et al.* isolated the first acyclic diaminocarbene (ADC) **61**. As in the case of the saturated NHC, there are steric limits within which dimerization can occur.⁷⁴ For example, ADC **99** and **100** tend to dimerize easily.¹¹⁶ The isolated ADC displayed several differences compared to typical NHCs: (i) the N-C-N bond angle is expanded 121° for **61** compared to 104° for **96**; (ii) increased σ -donation in transition metal complexes, and (iii)

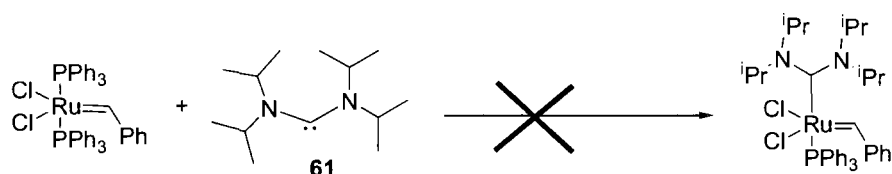
higher sensitivity to moisture. The increase in σ -donation is easily observed in their carbonyl complexes. The *cis*-dicarbonyl carbene rhodium(I) (Carbene-(CO)₂RhCl) complex shows $\nu(\text{CO})$ at 2057 cm⁻¹ for complex **93**, 2081 cm⁻¹ for complex **94** and 2076 cm⁻¹ for complex **95**. This trend in σ -donation also shows the higher basicity of ADCs compared to NHCs.⁹⁰

Figure 10: Structures of typical ADCs and NHCs and their transition metal complexes



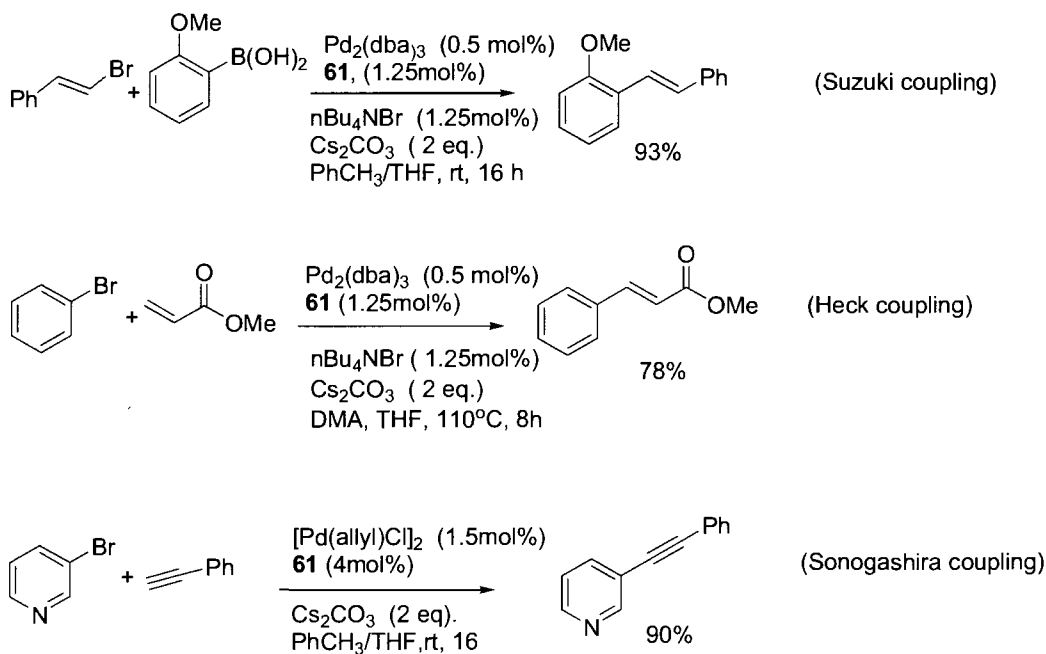
The space requirement due to the widened N-C-N angle, the increased reactivity that leads to dimerization and the enhanced reducing power of ADC pose a challenging problem in synthesis of the corresponding transition metals complexes. For example the incorporation of **61** in the Grubbs catalyst using the same method used for NHCs only led to decomposition (Equation 38).⁹⁰ However, it has been argued that introduction of ADCs into the Grubbs catalysts would expectedly increase the activities in olefin metathesis of these Ru catalysts. Therefore, synthetic methods to prepare the Ru complex should be further pursued in order to test this hypothesis.

Equation 38



Another disadvantage of ADC is that the reduction of metals such as tungsten and chromium carbonyl complexes has been observed. It should be noted however that other ADC-transition metal complexes such as rhodium, iridium, palladium complexes, that are relevant in catalysis, have been synthesized successfully.¹¹⁷ In terms of the application of ADC-metal complexes in catalysis, however, there has been limited interest; to date there has been only a few reports on their application in catalysis.^{118, 119} Prior work from our groups has shown the high reactivity of ADC-Pd complexes in cross-coupling reactions viz. Suzuki-Miyaura coupling, Heck coupling and Sonogashira coupling (Scheme 8).¹¹⁹ As expected, the putative catalyst showed remarkable stability to harsh conditions and high TON were observed. For example, the Heck coupling reaction was run at 110 °C for 8 hours. The current project to synthesize chiral ADC was designed as an extension to this work.

Scheme 8: ADC in Pd catalyzed coupling reactions

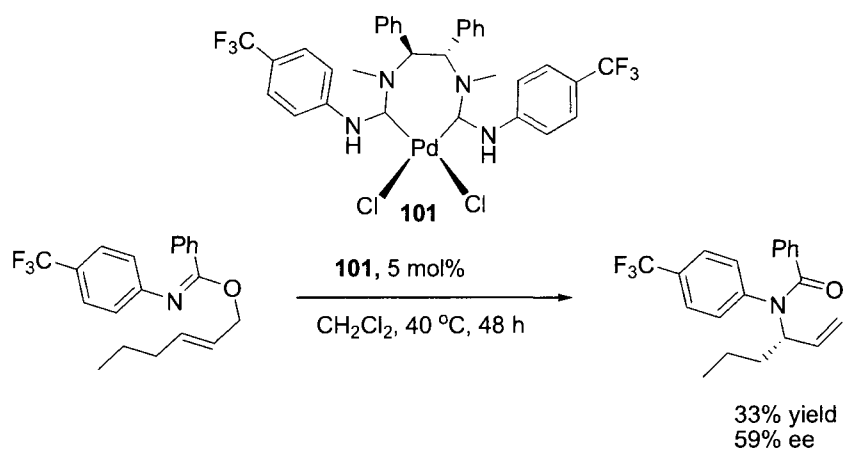


In a rare example of the use of a chiral ADC, Slaughter and coworkers reported that a chelating chiral bis-ADC, is an effective enantioselective catalyst for the Aza-Claisen

rearrangement.¹¹⁸ The bis-ADC chelator showed lower σ -donation than the bis-NCH and bis-phosphine bidentate ligand, and this is believed to be due to the congested coordination.¹²⁰

The attractiveness of ADCs over NHCs lies in the fact that a wide range of substituents on nitrogen can be used. This extends the potential scope of diaminocarbenes in transition metal catalysis

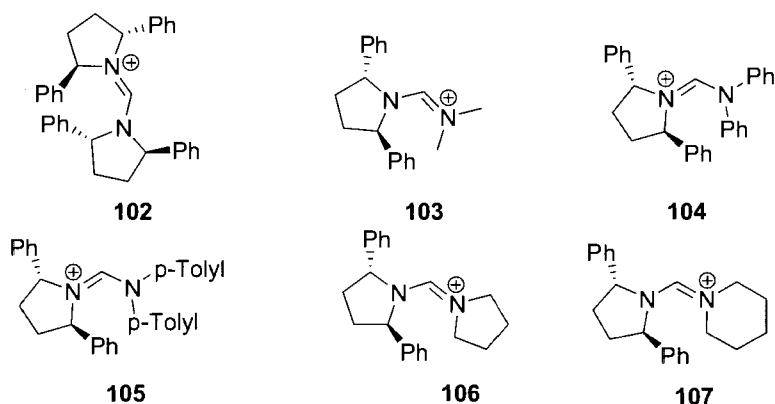
Scheme 9



1.2.3.2.1. *N,N,N',N'*-tetrasubstituted aminomethyleneiminium salts

We sought to generate chiral ADC from their corresponding formamidinium salts **102**-**107**. There are a number of ways to synthesize *N,N,N,N*-tetraalkylated formamidinium salts from secondary amines. A few of these methods are reviewed here next.

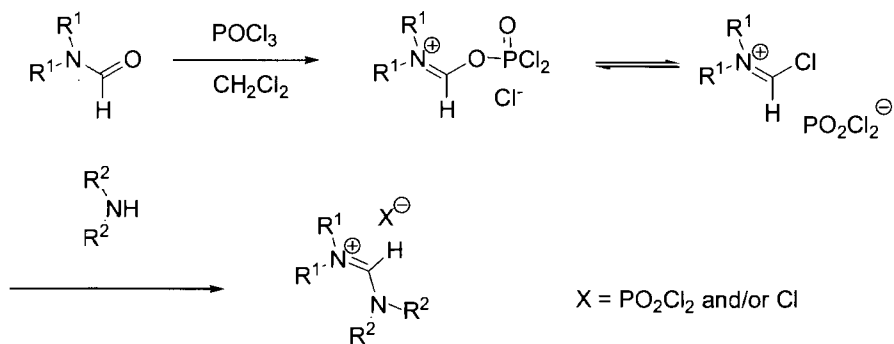
Figure 11



• Vilsmeier-Haack chemistry

The precursor to the first acyclic diaminocarbene isolated, bis(diisopropylamino) carbene, was synthesized via Vilsmeier-Haack method.⁷⁴ Chloroiminium salts are generated by reacting *N,N*-disubstituted formamide with halogenating reagents such as POCl_3 , PCl_5 , COCl_2 , ClCOOCCl_3 , and SOCl_2 . The chloroiminium salts (Vilsmeier reagents) are then trapped with the appropriate secondary amine to form the corresponding aminomethyleneiminium salts. In this process, HCl is generated and an equilibrium is generated between the secondary amines and the less reactive amide chloride adducts (Scheme 10). This problem is averted by either adding a neutralizing tertiary amine or pushing the equilibrium to the amine side provided the reaction can withstand these conditions.¹²¹

Scheme 10



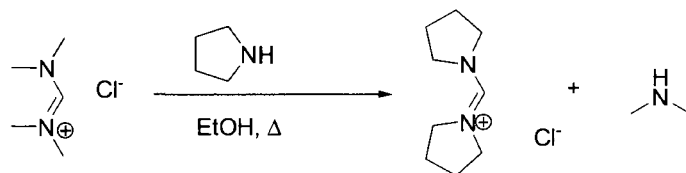
The isolation of the product has also been reported to be problematic due to the mixture of counterions in the product. However stable salts can be separated by column chromatography. Based on the fact anions such as iodide and perchlorates adducts have a reduced solubility, counterion exchange can also be used to access less soluble salts that can be isolated by crystallization. However, due to explosive reactivity of perchloric acid, sodium iodide is preferred, and it has been used in our lab to grow X-ray quality crystals.

- **Transamination**

Tetramethylaminomethyleneiminium salts have also been used for transamination. The dimethylamine group is substituted with other secondary amines such as pyrrolidine and piperidine at high temperatures in dry ethanol. The equilibrium is driven to the product side by the evaporation of dimethylamine from the reaction mixture (Equation 39).

This method is however restricted to less sterically hindered secondary amines (Equation 39). For example, the reaction with diisopropylamine did not proceed,¹²² and in our own hands 2,5-diphenylpyrrolidine **112** was also unreactive.

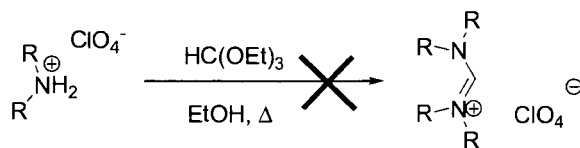
Equation 39



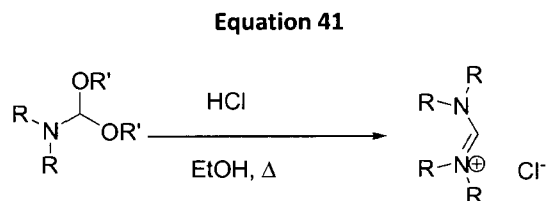
- **Orthoesters**

Although orthoesters work well for imidazolium and imidazolinium synthesis, it is not reactive enough for the synthesis of acyclic amidinium (Equation 40).¹²²

Equation 40

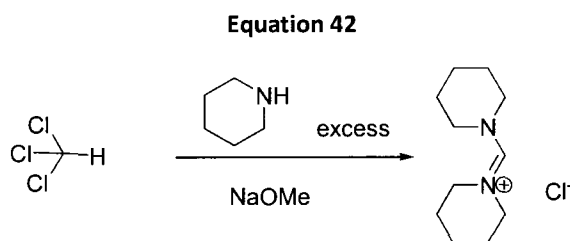


Similar to this method, amide acetals can also react with ammonium salts to form aminomethyleneiminium salts (Equation 41).¹²¹



- **Chloroform with excess secondary amines**

In the presence of alkoxide metals, chloroform reacts with excess secondary amines to form aminomethyleneiminium salts (Equation 42).¹²¹



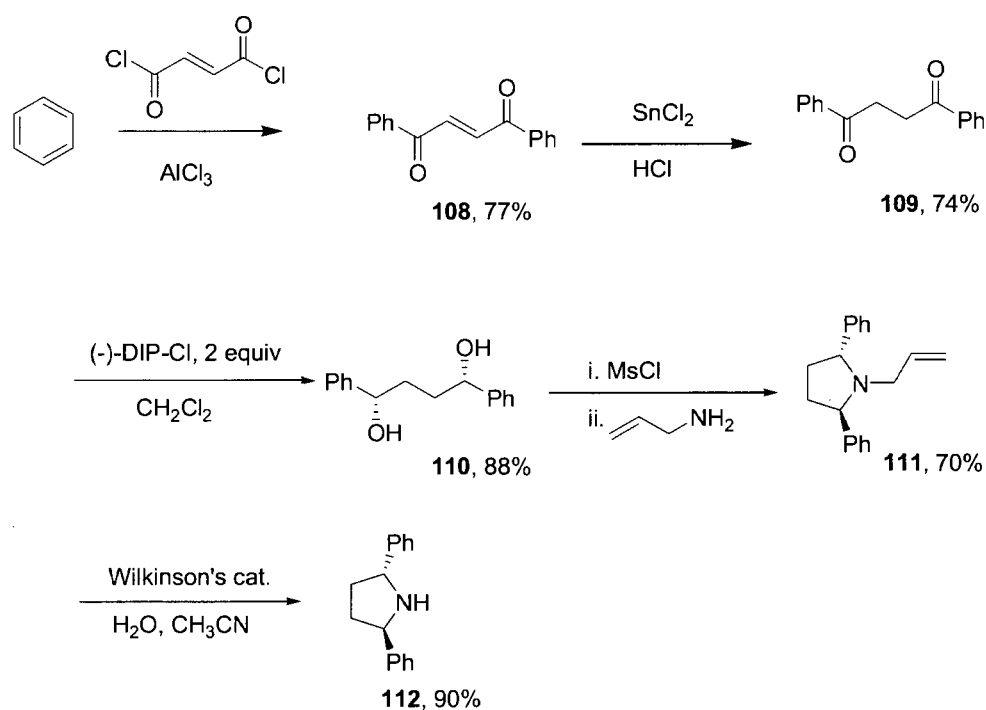
2. Discussion.

In order to synthesize both C₂ and C₁-symmetric ADC precursors (**102-107**) we required the synthesis of the enantioenriched 2,5-diphenylpyrrolidine **112**, which was synthesized as shown in Scheme 11.^{123, 124}

The diketone **109** was obtained by tin(II) reduction of **108**, which was easily obtained through Friedel-Crafts reaction from benzene and fumaryl chloride. Since we required enantioenriched material, we reduced the diketone **109** with DIP-Cl,¹²⁵ a method which presented a number of potential drawbacks. DIP-Cl is quite sensitive to moisture, and it requires extreme care in handling, which is hindered by its capricious solid-liquid phase change. It has a reported melting point range of 53-55 °C, but as soon as it is taken out the fridge it starts to melt to a viscous gel, which makes the weighing and transferring to the reaction vessel difficult to accomplish. In addition, the DIP-Cl reduction works fairly well on a

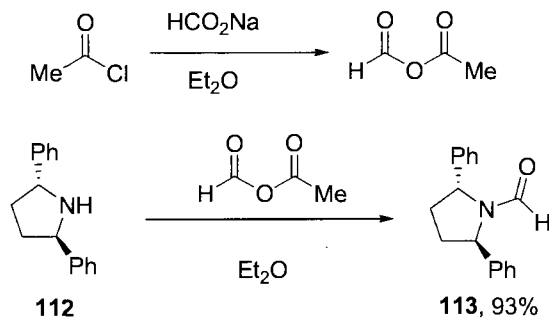
small scale, but the conversions become very low at larger reaction scales. The isolation of the final product **110** from stoichiometric pinene is also problematic. Nevertheless, diol **110** was subsequently reacted with mesyl chloride, and cyclized through a double S_N2 substitution with allyl amine to afford the *N*-allyl-2*R*,5*R*-diphenylpyrrolidine **111**, and the allyl substituent was ultimately removed via treatment with Wilkinson's catalyst to furnish **112**.

Scheme 11



We also required the *N*-formyl-2,5-diphenylpyrrolidine **113**, and we obtained this compound through a simple reaction of **112** with acetic formic anhydride (Scheme 12).¹²⁶ The acetic formic anhydride was synthesized from sodium formate and acetyl chloride following the procedure reported by Krimen.¹²⁷

Scheme 12

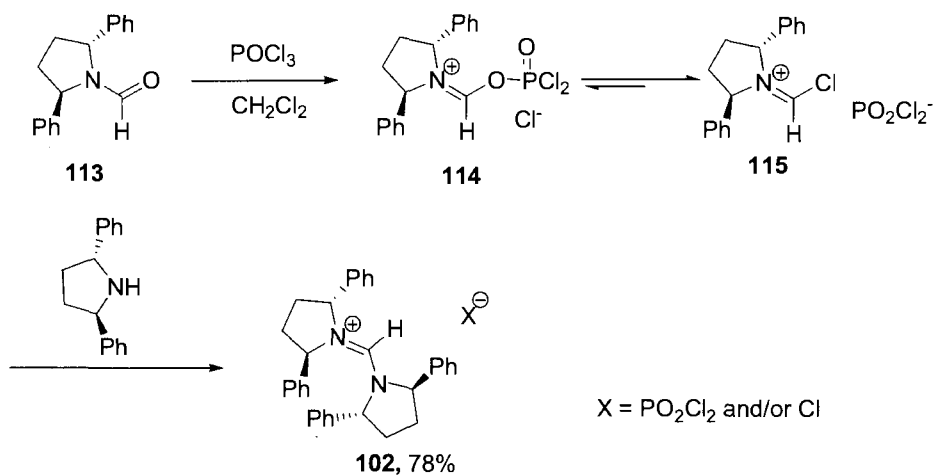


We then moved on to the synthesis of the formamidine salts. All the formamidine salts were synthesized through Vilsmeier-Haack chemistry. Generally, the *N*-formyl amines react with POCl_3 to give the corresponding chloromethyleneiminium PO_2Cl_2^- salts; these salts are used *in situ* due to their reactivity towards moisture. Primary and secondary amines react with the Vilsmeier reagents to form aminomethyleneiminium salts and hydrochloric acid, which can be neutralized with the addition of a base to the reaction mixture.

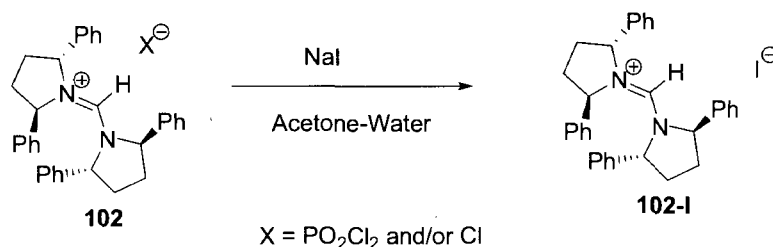
The preparation of the C_2 -symmetric formamidine **102**, which was the first to be synthesized, is presented in Scheme 13. The counterion could not be determined unambiguously (both Cl^- and PO_2Cl_2^- were equally possible). The yields (calculated on the basis of the POCl_2^- anion) however, were excellent and the ^1H NMR did not suggest the presence of the mixture. The aqueous work up of this mixture, however, always led to the hydrolysis of the formamidine to give a 1:1 mixture of formamide **112** and secondary amine. To avoid this outcome, the crude mixture was simply dried up *in vacuo* and run on silica gel (eluted with 10% MeOH: CH_2Cl_2 mixture). Some of the salts (**102**, **104** and **105**) seemed to afford dark intractable low melting point products, which we attribute to the presence of counterion mixtures and also to their hygroscopic nature. We tried the counterion exchange of **102** with NaBF_4 , but the exchange was not complete, as suggested by ^1H NMR spectrum (two amidinium protons were observed, one at 9.7 ppm and another at 8.7 ppm). We later realized that iodide counterion exchange could be achieved with greater success and since the corresponding formamidine salts had a decreased solubility, better

isolation of **102** was achieved. Colorless X-ray quality crystals of the iodide crystals were grown by a slow evaporation of the ethylacetate, dichloromethane solution.

Scheme 13

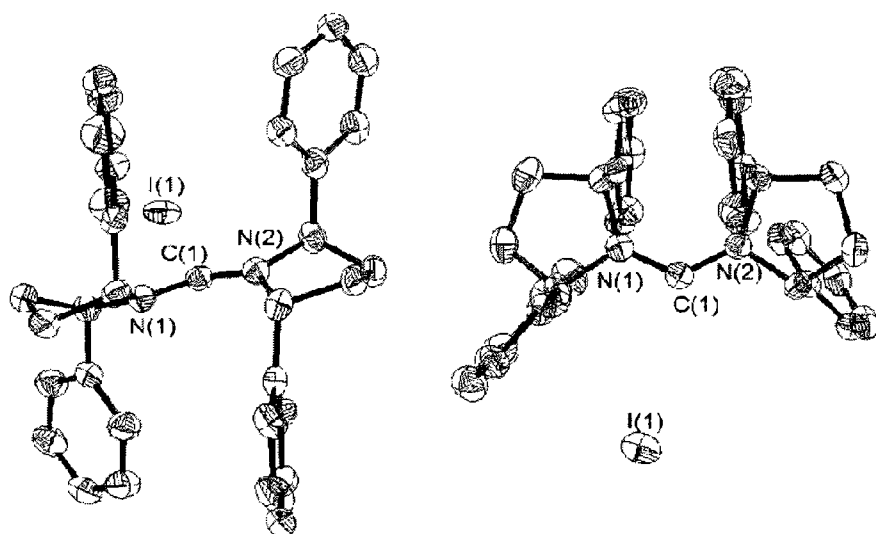


Equation 43



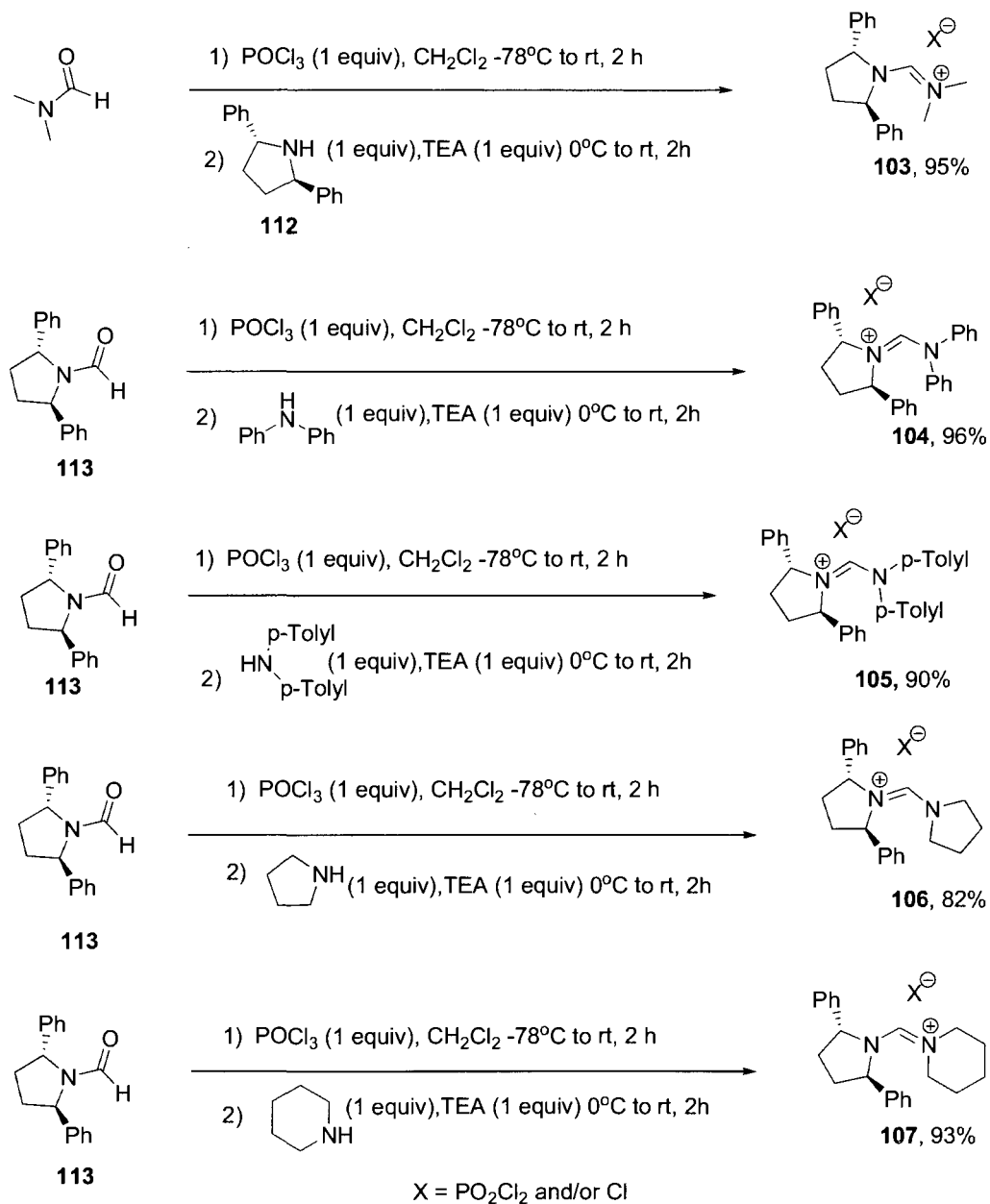
The crystal structure was solved by Dr. Charles Macdonald's group (Ben Cooper and approved by Dr. Macdonald). The crystal structure (Figure 12) reveals a N-C-N angle of 127.70°, which is considerably smaller than the reported 133.24° for diisopropylaminomethylidene(diisopropyl)ammonium trifluoromethanesulfonate.⁹⁰ The crystal structure also show a slightly distorted C₂-symmetry, with the phenyl rings at the top disposed parallel to each other above and below the N-C-N plane. C₁-symmetric ADC precursors, **103-107**, were also synthesized as shown in Scheme 14.

Figure 12: Ortep 3 crystal structure of the 102-I at 50% thermal ellipsoids



Although the isolation of free ADC or the isolation of the corresponding transition metal complexes has not yet been forthcoming, a considerable amount of information has been gathered. Acyclic diaminocarbene precursors (formamidine salts) have much lower acidities than their cyclic congeners. This has been observed when we tried to synthesize silver-**116** and copper-**116** complexes using silver oxide or copper oxide. In the case of silver oxide the formamidine were hydrolyzed to the N-formyl amine and secondary amine. When we tried copper oxide, no reaction occurred. The deprotonation using either NaH or KO^tBu were also not successful.

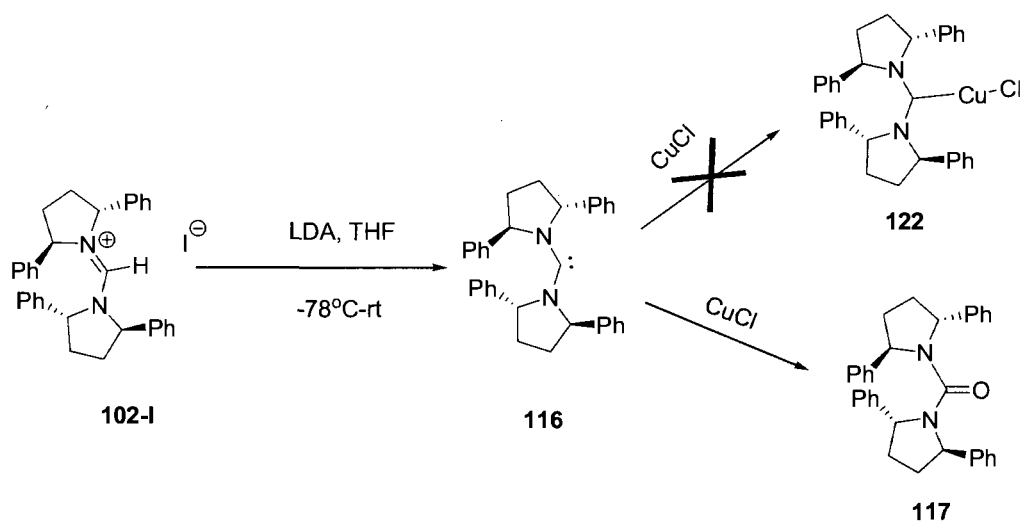
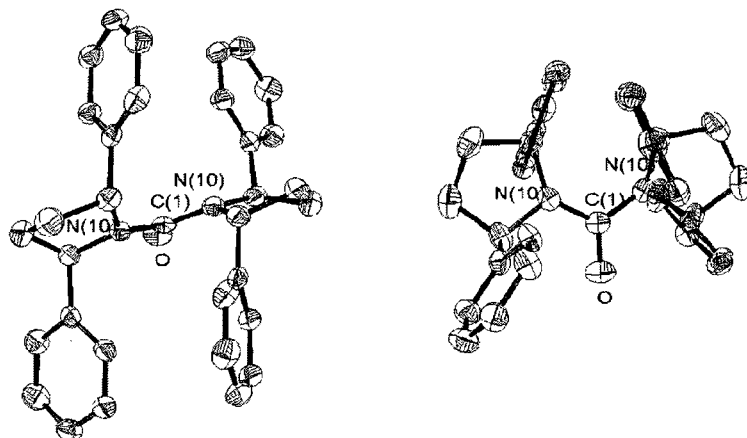
Scheme 14



LDA, however, does affect the deprotonation of the formamidinium **102**. When we tried to synthesize the **116**-Cu complex the urea **117** was instead isolated (Scheme 15). We

believe the carbene **116** is formed *in situ* but is quickly oxidized in presence of oxygen to form **117**, in agreement with what has been observed previously by Wanzlick.⁵⁹ An X-ray quality crystal was grown and the structure was solved by Ben Cooper and Dr. Charles Macdonald. This realization is quite promising in that the complete exclusion of oxygen should enable the free carbene to be isolated and subsequent trapping with transition metals should also be possible.

Scheme 15

Figure 13: Ortep crystal structure of **117**, thermal ellipsoids shown at 50% probability

3. Conclusion and future work

We have synthesized a number of chiral ADC precursors and their isolation and synthesis of their transition metal complexes studies has been initiated. In addition to our interest in isolating the free ADC and their Cu, Pd, and Rh complexes, there is an ongoing study of the enantioselective activities of the catalysts generated *in situ*. Our interest mainly focuses on the following reactions shown in: Heck cross-coupling, hydrosilylation/hydrogenation of ketones, and 1,4 conjugate additions.

4. Experimental.

General notes:

All reactions were carried out under nitrogen atmosphere and solvents were dried by using standard techniques. All secondary amines and secondary formamides were obtained from Sigma Aldrich and were used as received except *R,R*-2,5-diphenylpyrrolidine and *R,R*-*N*-formyl-2,5-diphenylpyrrolidine, which were synthesized according to the reported procedures.¹²³⁻¹²⁵

General procedure to synthesize formamidinium salts:¹²²

The formamidinium salts were synthesized through Vilsmeier-Haack chemistry according to a modified procedure reported by Alder *et al.* To a solution of an appropriate secondary formamide in dry dichloromethane was added one equivalent of POCl₃ at -78 °C and the mixture was allowed to warm to room temperature and stirred for two hours. The mixture was cooled to 0 °C and a solution of one equivalent of an appropriate secondary amine and one equivalent of triethylamine in dichloromethane was added, it was again allowed to warm to room temperature and stirred for two hours. The solvent was removed *in vacuo* and the crude product was run on a silica gel column eluting with 10% MeOH/CH₂Cl₂.

Counterion exchange with tetrafluoroborate

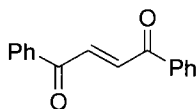
The formamidinium salts purified by silica gel chromatography were shaken with a concentrated aqueous solution of tetrafluoroborate and extracted with dichloromethane four times. The combined dichloromethane extracts were then dried with magnesium sulfate, filtered, and dried *in vacuo*.

Counterion exchange with iodide

The chromatographed formamidinium salt was dissolved in acetone and poured in a separatory funnel. It was then shaken with a concentrated aqueous solution of NaI and dichloromethane was added to give two layers. The aqueous layer was then extracted three times with dichloromethane. The organic layers were then combined, dried with MgSO₄, filtered over a celite pad, and concentrated *in vacuo*.

Characterization data

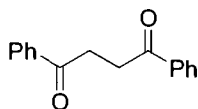
- **(E)-1,4-diphenylbut-2-ene-1,4-dione**



108

A solution of 54.2 g of AlCl₃ in 300 ml benzene in a 3-necked round bottom flask equipped with a stir bar, a condenser attached to a trap containing 20 ml of 2N NaOH and a dropping funnel charged with fumaryl chloride was heated to 60 °C with an oil bath. The oil bath was then removed and 24 g of fumaryl chloride was added dropwise with stirring, to prevent a rapid HCl_(g) evolution. After the addition is complete, the solution mixture was stirred for 20 minutes and then poured on ca. 800 g of ice. After the ice has all melted, the two layers were separated and the organic layer washed 3 times with warm water. The organic layer was concentrated by distillation at reduced pressure. The residue was triturated with ethanol to afford yellow crystals that were isolated by suction filtration in 77% yield.

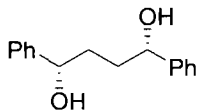
- **1,4-diphenyl-2,5-butanedione**



109

A hot solution of 27 g of (*E*)-1,4-diphenylbut-2-ene-1,4-dione in 140 ml of ethanol was poured onto a hot solution of 27 g of SnCl₂ in 42 ml of 8N HCl and 14 ml of ethanol. The mixture was diluted immediately with 25 ml of water and filtered. The recrystallization from ethanol furnished white crystals in 74% yield. ¹H NMR δ: 8.1-8.03 (m, 4H), 7.6-7.3 (m, 6H), 3.5 (s, 4H).

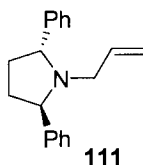
- **(*S,S*)-1,4-diphenyl-2,5-butanediol**



110

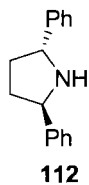
Into a round bottom flask containing 31 g of (-)-DIP-Cl and 10 g of 1,4-diphenyl-2,5-butanedione at -78 °C was added THF slowly and the mixture was stirred for 2 hours at this temperature. Mechanical stirring and temporarily removing the solution from the cooling bath was needed to help with the mixing. The mixture was then stirred for 14 hours. The solvent was removed *in vacuo* and the mixture attached to a high vacuum pump was stirred for 24 hours at 40-60 °C to remove excess pinene. Diethanol amine and diethyl ether were added to the residue at 0 °C, the mixture is stirred for 30 minutes at this temperature, as before mechanical stirring was required. The mixture was allowed to warm to room temperature and stirred for 12 hours. The mixture was filtered; the filtrate was concentrated and purified by silica gel chromatography 1:1 hexanes: diethyl ether followed by 1:3 hexanes: diethyl ether; 88% of product was obtained after removal of solvent *in vacuo*; ¹H NMR δ: 7.27-7.15 (m, 10H), 4.49 (s, br, 2H), 2.41 (d, 2H), 1.88-1.70 (m, 4H).

- **(2*R*, 5*R*)-*N*-allyl-2,5-diphenylpyrrolidine**



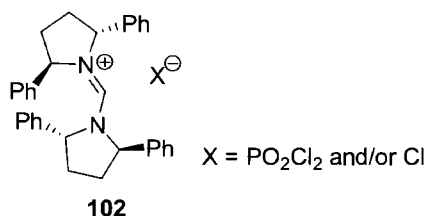
To a solution of mesyl chloride in dichloromethane at $-20\text{ }^{\circ}\text{C}$ was added a solution of 5.2 (5*S*)-1,4-diphenyl-2,5-butanediol and triethylamine in dichloromethane. The reaction mixture was stirred at this temperature for 2 hours, quenched with NH_4Cl and allowed to warm to room temperature. The organic layer was concentrated, to approximately 20ml, and dissolved in ethyl acetate. The mixture was washed with saturated with 1:2:1 water: brine: saturated sodium bicarbonate, and with sodium bicarbonate. The organic layer was dried with sodium sulphate anhydrous concentrated to approximately 20 ml. The residue was then triturated with hexane at $0\text{ }^{\circ}\text{C}$ to induce precipitation. The solvent was decanted and the white crystals in residual n-hexanes were used in the next step. Due to instability of this compound, no proper isolation was done. After the solvent was decanted, the white crystals were dissolved in allylamine at $0\text{ }^{\circ}\text{C}$ and allowed to slowly warm to room temperature and stirred overnight. Allyl amine was removed *in vacuo* and the residue was dissolved in diethyl ether, washed with saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulphate anhydrous, filtered and concentrated. The resulting yellow oil was purified on silica gel column, eluted with 30:1 hexane: diethyl ether to give clear oil (70% from **110**). A small forerun of this column consists of a mixture of diastereomers. ^1H NMR δ : 7.35-7.2 (m, 10 H), 5.8-5.50 (m, 1 H), 4.96-4.88 (m, 2 H), 3.40-3.30 (m, 2 H), 3.05-2.92 (m, 1 H), 2.80-2.70 (m, 1 H), 2.60-2.45 (m, 2 H), 2-1.90 (m, 2 H).

- **(*R*, *R*)-2,5-diphenylpyrrolidine**



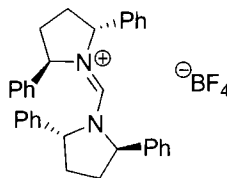
In a 500 ml 3-necked round bottom flask equipped with a dropping funnel, reflux condenser, and a distillation head; **111** and Wilkinson's catalyst were dissolved in 84:16 w/w acetonitrile: water. The solution was purged with N₂ gas and heated to boil. The solvent level was maintained by adding more through the dropping funnel. After 3 hours, the reaction mixture was cooled to room temperature and dissolved in ether. The organic layer was washed with brine and the combined aqueous layer was back-extracted with ether. The combined organic layer was then dried over sodium sulphate, concentrated and purified by silica with 1:1 hexane:ether as eluent system. After removal of the solvent the product was obtained in 90% yield; ¹H NMR δ: 7.40-7.10 (m, 10 H), 5.6-5.4 (m, 2 H), 2.35-2.29 (m, 2 H), 1.99 (br, 1 H), 1.85-1.75 (m, 2 H).

- ***R,R,R,R*-2,5-diphenylpyrrolidin-1-ylmethylene(2,5-diphenylpyrrolidinium) ion**



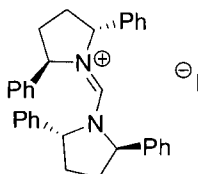
The compound was prepared from *R,R*-*N*-formyl-2,5-diphenylpyrrolidine and *R,R*-2,5-diphenylpyrrolidine to give a low melting yellow solid in 78% yield. ¹H NMR [CDCl₃, 500 MHz] δ: 9.67 (s, 1 H), 7.44-7.37 (m, 6 H), 7.20-7.13 (m, 10 H), 6.78-6.76 (m, 4 H), 5.92-5.90 (m, 2 H), 4.95-4.93 (m, 2 H), 2.34-2.20 (m, 4 H), 1.68-1.60 (m, 4 H); ¹³C NMR [CDCl₃, 75 MHz] δ: 155.81, 140.95, 140.88, 130.17, 129.08, 128.96, 128.30, 126.33, 124.89, 70.88, 64.63, 33.59, 29.65.

- ***R,R,R,R*-2,5-diphenylpyrrolidin-1-ylmethylene(2,5-diphenylpyrrolidinium) BF₄⁻**

**102-BF₄**

102 in dichloromethane was shaken in a separatory funnel with a concentrated solution of tetrafluoroborate and extracted with dichloromethane four times. The combined dichloromethane extracts were then dried with magnesium sulfate, filtered and dried *in vacuo* to afford a dark red low melting point solid. ¹H NMR [CDCl₃, 500 MHz] δ: 8.35 (s, 1 H), 7.49-7.41 (m, 6 H), 7.23-7.14 (m, 10 H), 6.77-6.76 (m, 4 H), 5.52-5.50 (m, 2 H), 4.97-4.95 (m, 2 H), 2.33-2.23 (m, 4 H), 1.72-1.67 (m, 4 H); ¹³C NMR [CDCl₃, 75 MHz] δ: 154.07, 140.64, 140.06, 130.26, 129.23, 128.71, 126.42, 124.81, 71.40, 64.97, 33.92, 30.33.

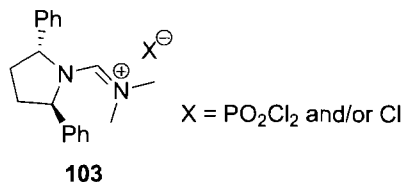
- ***R,R,R,R*-2,5-diphenylpyrrolidin-1-ylmethylene(2,5-diphenylpyrrolidinium) I⁻**

**102-I**

The compound was prepared from *R,R*-*N*-formyl-2,5-diphenylpyrrolidine and *R,R*-2,5-diphenylpyrrolidine, the chromatographed product was dissolved in acetone poured in a separatory and shaken with a concentrated aqueous solution of sodium iodide, and extracted with dichloromethane four times. The combined dichloromethane extracts were dried with magnesium sulfate, filtered and dried *in vacuo*. Recrystallization from ethylacetate and dichloromethane gave colorless needles, mp: 191-194 °C. ¹H NMR [CDCl₃, 500 MHz] δ: 9.27 (s, 1 H), 7.58-7.55 (m, 6 H), 7.30-7.15 (m, 10 H), 6.90-6.88 (m, 4 H), 6.06-6.04 (m, 2 H), 5.07-5.04 (m, 2 H), 2.42-2.35 (m, 4 H), 1.80-1.70 (m, 4 H); ¹³C NMR [CDCl₃, 75

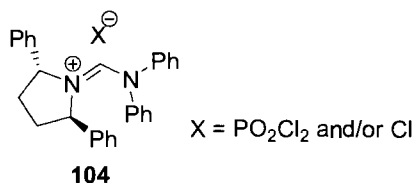
MHz] δ : 154.31, 140.77, 140.35, 130.23, 129.22, 129.10, 128.53, 126.51, 124.95, 70.67, 64.80, 33.65, 30.01.

- ***R,R*-2,5-diphenylpyrrolidin-1-ylmethylene(*N,N*-dimethylammonium) ion**



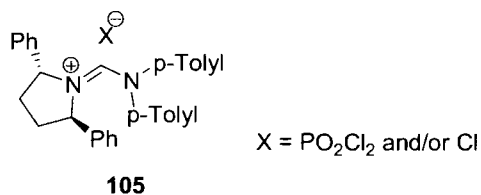
103 was prepared from *N,N*-dimethyl formamide and *R,R*-2,5-diphenylpyrrolidine to give a low melting point clear yellow solid in 95% yield. ^1H NMR [CDCl_3 , 300 MHz] δ : 8.43 (s, 1 H), 7.39-7.19 (m, 10 H), 5.99-5.97 (m, 2 H), 3.12 (s, 3 H), 2.93 (s, 3), 2.71-2.69 (m, 1 H), 2.34-3.32 (m, 1 H), 1.89-1.86 (m, 2 H). ^{13}C NMR [CDCl_3 , 75 MHz] δ : 156.32, 141.28, 140.75, 129.66, 129.21, 128.30, 126.77, 125.10, 69.89, 64.54, 46.36, 39.02, 34.82, 30.10.

- ***R,R*-(*N,N*-diphenylamin)-*N*-ylmethylene(2,5-diphenylpyrrolidinium) ion**



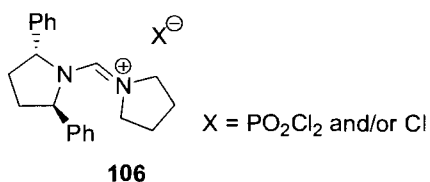
104 was prepared from *R,R*-*N*-formyl-2,5-diphenylpyrrolidine and *N,N*-diphenyl amine, and a low melting point dark brown solid was obtained in 96% yield. ^1H NMR [CDCl_3 , 500 MHz] δ : 9.08 (s, 1 H), 7.60-7.55 (m, 5 H), 7.44-7.39 (m, 3 H), 7.33-7.31 (m, 4 H), 7.26-7.23 (m, 4 H), 7.17-7.16 (m, 3 H), 6.95-6.93 (m, 1 H), 5.92-5.90 (d, 1 H), 4.62-4.59 (m, 1 H), 2.62-2.54 (m, 2 H), 2.06-1.96 (m, 2 H); ^{13}C NMR [CDCl_3 , 75 MHz] δ : 153.14, 143.23, 140.78, 138.52, 137.87, 129.97, 129.86, 129.72, 129.46, 129.38, 129.11, 128.94, 128.79, 128.04, 127.52, 126.57, 125.15, 124.45, 71.57, 67.42, 36.08, 32.01.

- ***R,R*-(*N,N*-di-*p*-tolylamnin)-*N*-ylmethylene(2,5-diphenylpyrrolidinium) ion**



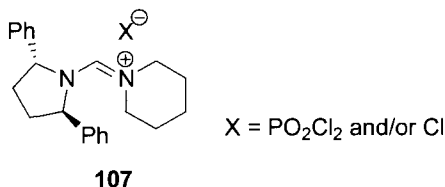
105 was prepared from *R,R*-*N*-formyl-2,5-diphenylpyrrolidine and *N,N*-di-*p*-tolyl amine, and a low melting point dark red solid was obtained in 97% yield. ^1H NMR [CDCl_3 , 300 MHz] δ : 8.13 (s, 1 H), 7.63-7.53 (m, 2 H), 7.53-7.42 (m, 3 H), 7.36-7.28 (m, 3 H), 7.22-7.16 (m, 3 H), 7.03-6.93 (m, 5 H), 6.68-6.66 (m, 1 H), 6.08-6.04 (m, 1 H), 5.78-5.75 (m, 1 H), 4.92- 4.87 (m, 1 H), 2.70-2.63 (m, 1 H), 2.54-2.47 (m, 1 H), 2.39 (s, 3 H), 2.19 (s, 3 H), 1.97-1.90 (m, 1 H); ^{13}C NMR [CDCl_3 , 75 MHz] δ : 152.30, 141.05, 140.61, 139.80, 139.15, 138.60, 135.40, 130.48, 129.80, 129.71, 129.06, 127.99, 127.63, 127.11, 126.38, 125.01, 124.07, 121.71, 71.85, 67.30, 36.14, 32.28, 21.30, 20.92.

- ***R,R*-2,5-diphenylpyrrolidin-1-ylmethylenepyrrolidinium ion**



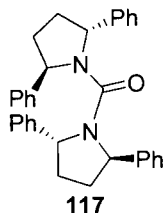
106 was prepared from *N*-formyl pyrrolidine and *R,R*-2,5-diphenylpyrrolidine to form a clear yellow low melting point solid in 82% yield. ^1H NMR [CDCl_3 , 500 MHz] δ : 9.00 (s, 1 H), 7.46-7.31(m, 10 H), 6.04-6.03 (d, 1 H), 5.82-5.80 (d, 1 H), 4.03-4.01 (m, 1 H), 3.85-3.83 (m, 1 H), 3.63-3.61 (m, 1 H), 3.05-3.03 (m, 1 H), 2.76-2.74 (m, 1 H), 2.44-2.42 (m, 1 H), 1.98-1.65 (m, 6 H); ^{13}C NMR [CDCl_3 , 75 MHz] δ : 152.94, 141.25, 140.93, 129.82, 129.49, 128.63, 128.34, 127.00, 124.89, 69.52, 64.26, 55.40, 48.42, 34.41, 30.44, 25.87, 23.69.

- R,R*-2,5-diphenylpyrrolidin-1-ylmethylenepiperidinium ion**

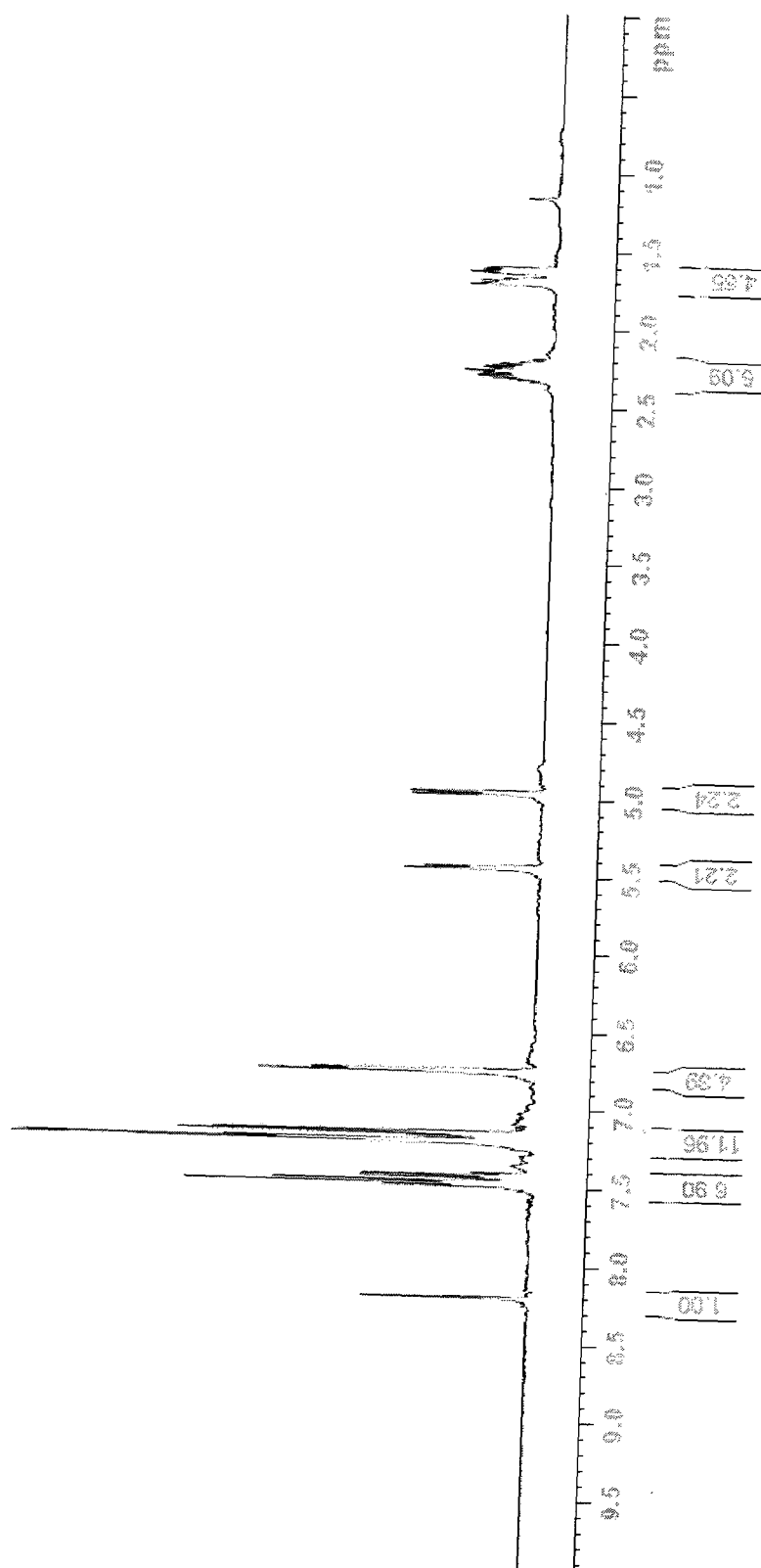
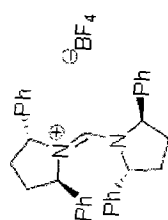


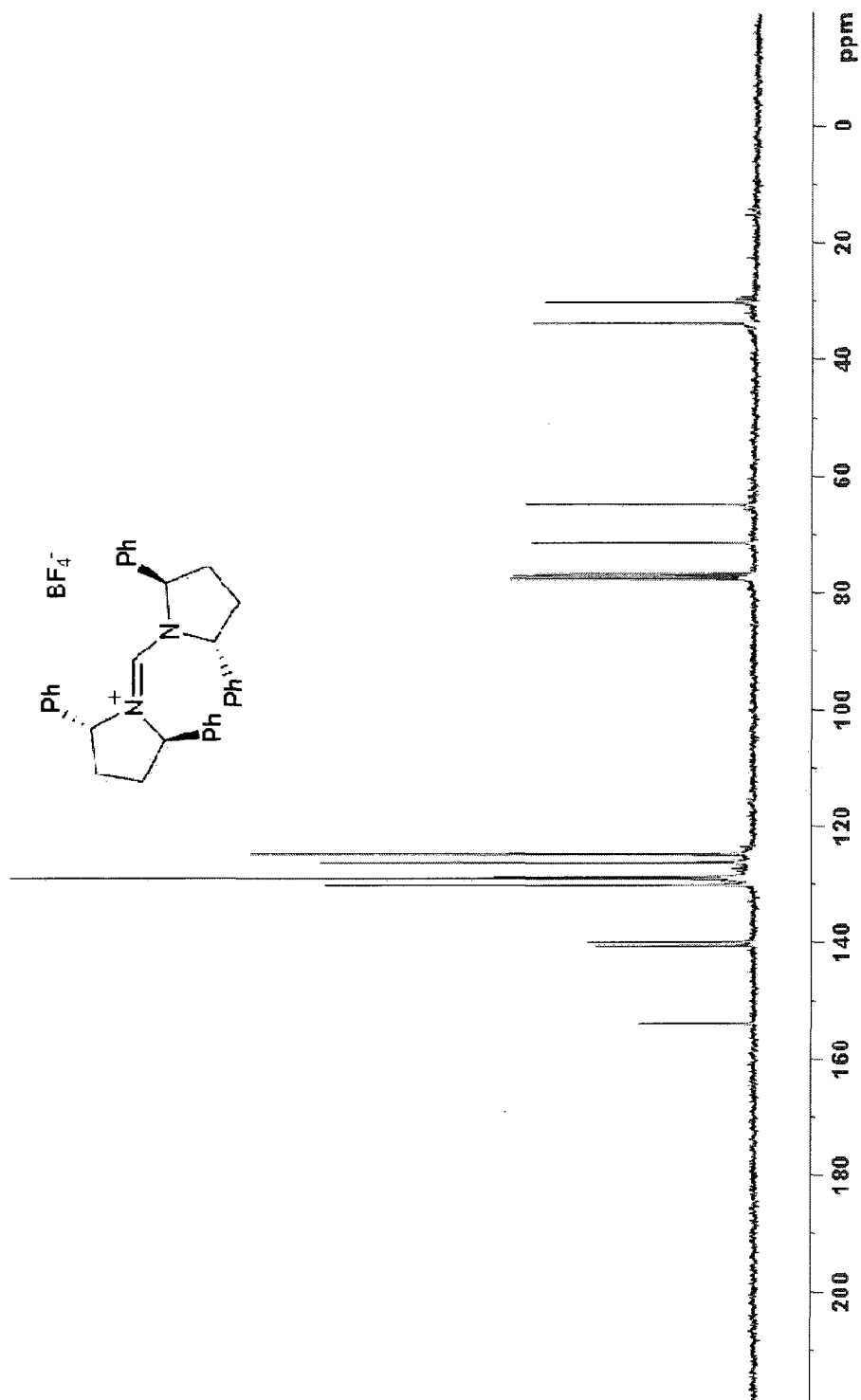
107 was synthesized from *N*-formyl piperidine and *R,R*-2,5-diphenylpyrrolidine to form a clear yellow low melting point solid in 93% yield. ¹H NMR [CDCl₃, 300 MHz] δ: 8.97 (s, 1 H), 7.47-7.27 (m, 10 H), 6.22-6.20 (d, 1 H), 5.59-5.56 (d, 1 H), 3.78-3.74 (m, 1 H), 3.54-3.42 (m, 2 H), 3.33-3.29 (m, 1 H), 2.57-2.54 (m, 1 H), 2.30-2.28 (m, 1 H), 2.02-1.99 (m, 2 H), 1.65-1.61 (m, 2 H), 1.42-1.40 (m, 2 H), 1.24-1.19 (m, 1 H), 0.54-0.50 (m, 1 H); ¹³C NMR [CDCl₃, 75 MHz] δ: 153.61, 141.31, 139.41, 129.61, 129.16, 128.35, 128.23, 126.66, 125.65, 70.29, 64.85, 56.04, 48.64, 35.15, 30.20, 26.09, 24.73, 22.84.

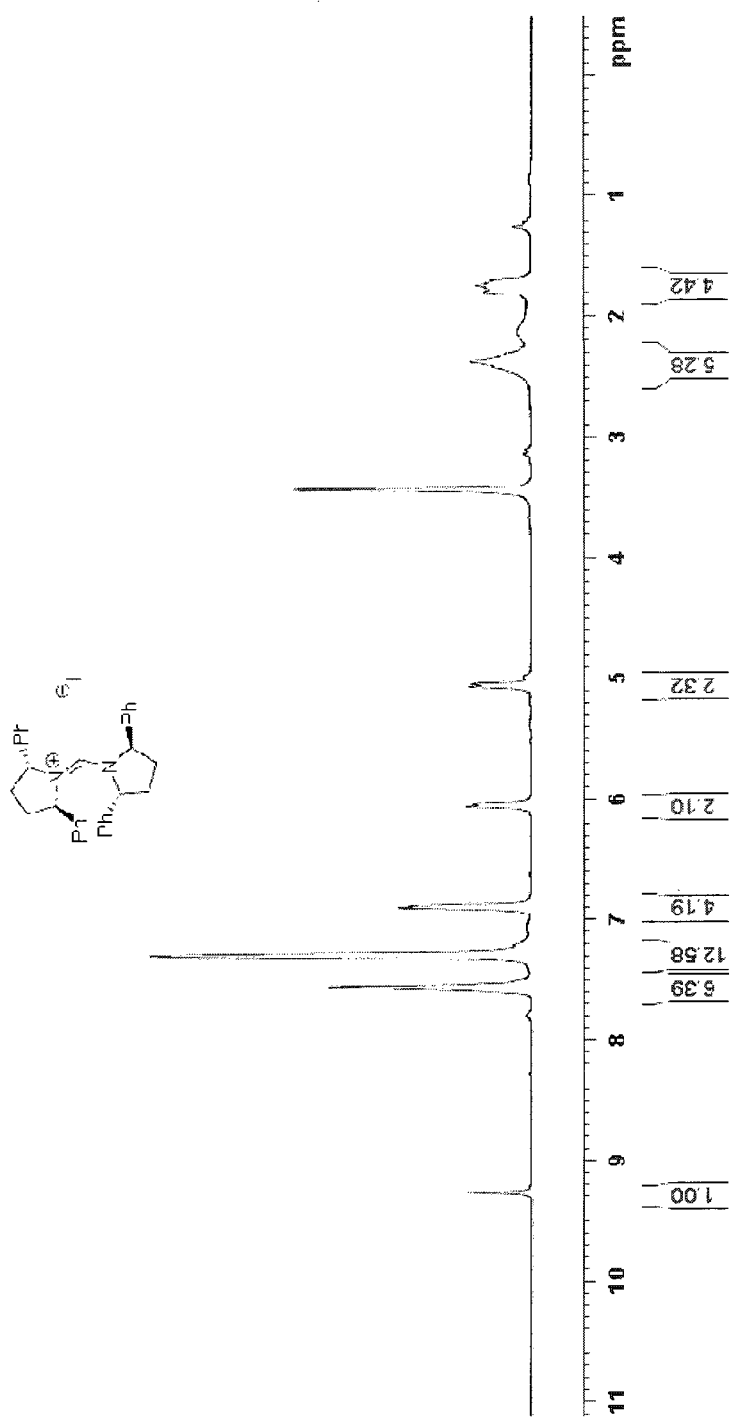
- Bis(*R,R*-2,5-diphenylpyrrolidin-1-yl)methanone**

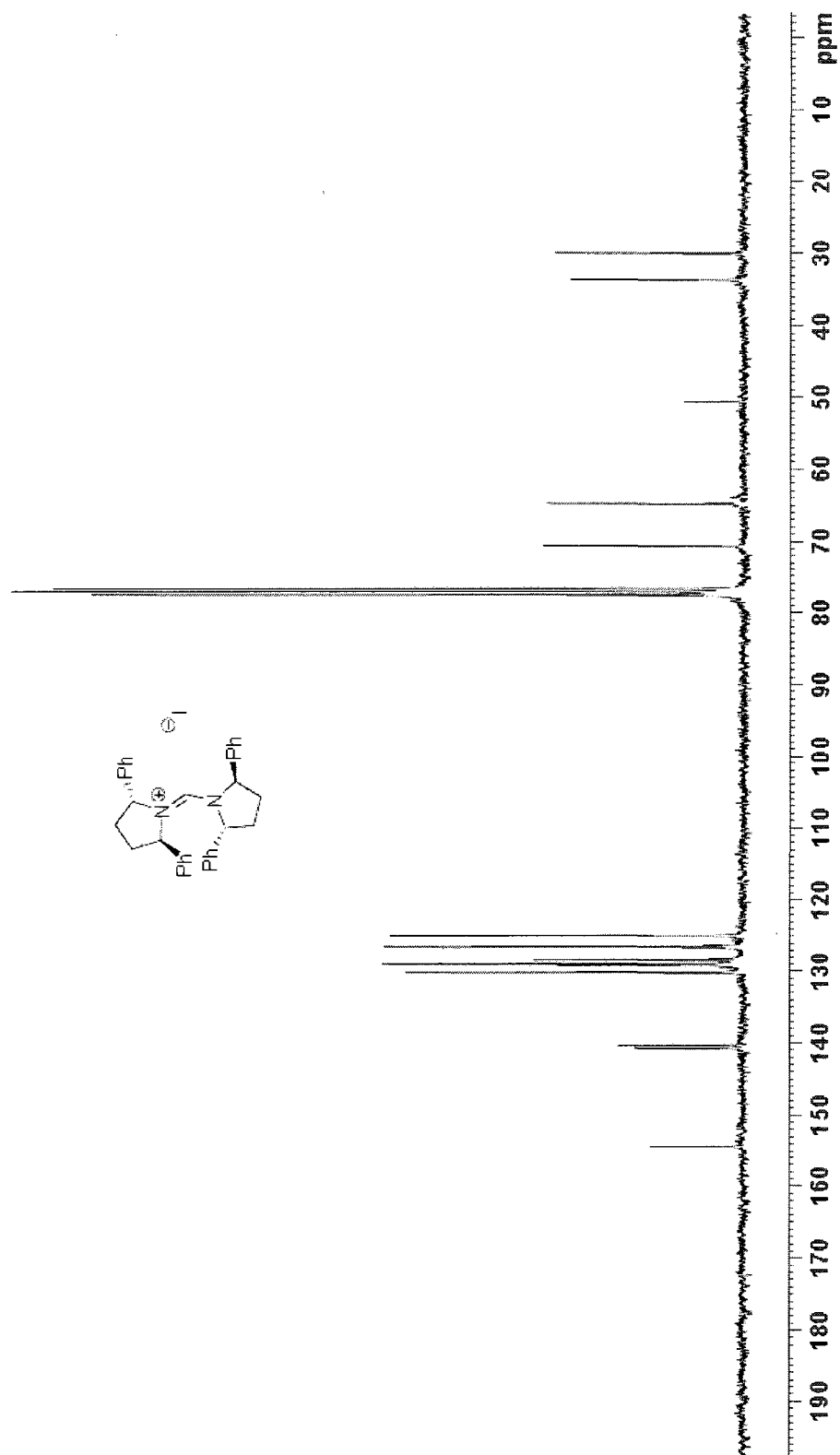


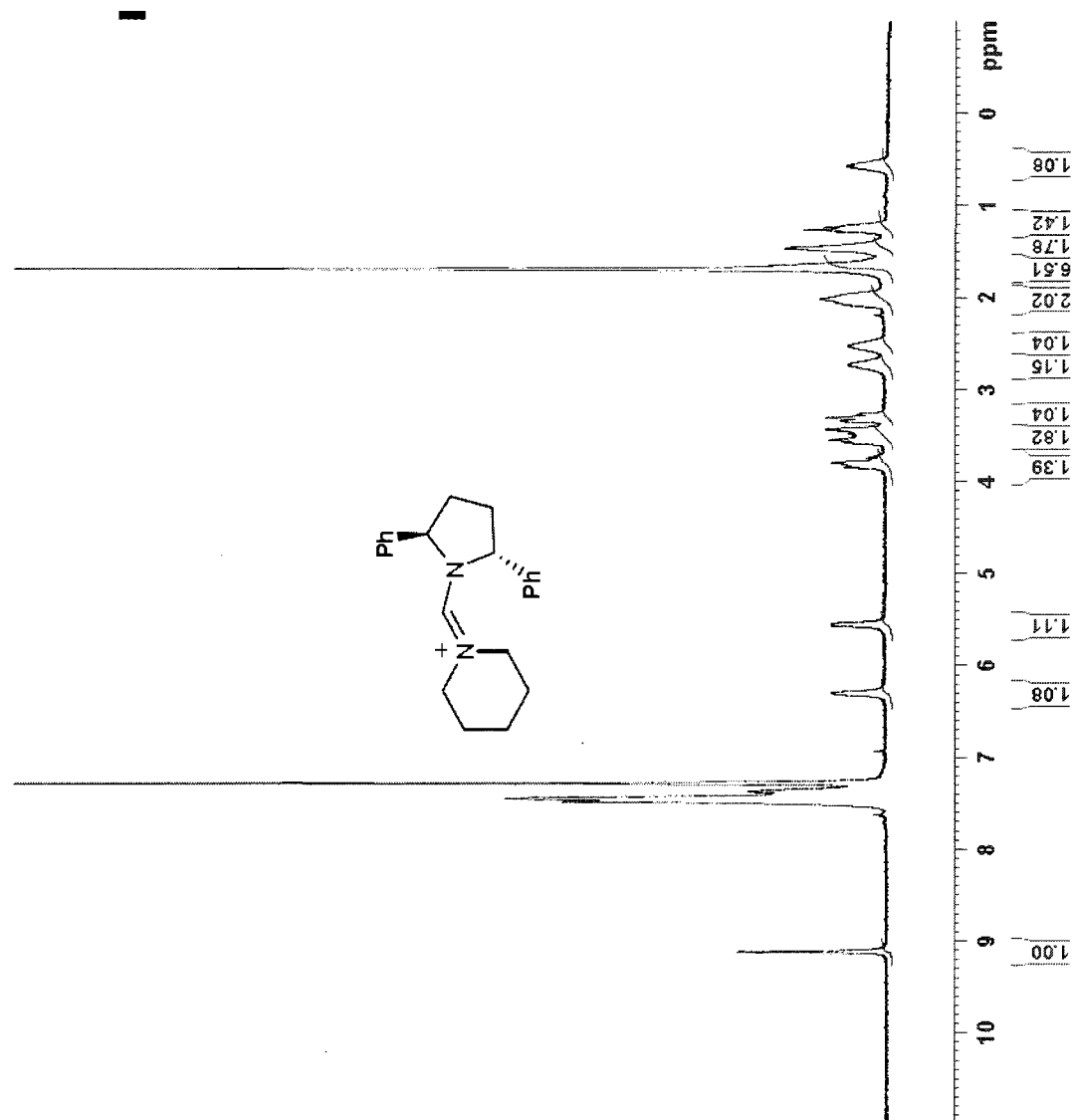
A solution of the formamidine **102-I** salt and CuCl in THF, was first stirred for thirty minutes with oven dried 4Å MS, the mixture was then cooled to -78 °C and one equivalence of LDA in hexane-THF solution, the mixture was allowed to warm to room temperature, and stirred for 30 minutes and dried *in vacuo*. The crude product was recrystallized from ethyl acetate in open air to give clear needles, mp: >280 °C; ¹H NMR [CDCl₃, 300 MHz] δ: 7.50-7.35 (m, 6H), 7.32-7.27 (m, 4H), 7.10-7.07 (m, 6H), 6.55-6.52 (m, 4H), 2.23-2.21 (m, 4H), 1.65 (m, 2H), 1.37 (m, 2H) (Note: 2 protons unobserved); ¹³C NMR [CDCl₃, 75 MHz] δ: 156.68, 145.31, 144.91, 130.36, 129.59, 129.05, 128.65, 128.40, 128.02, 127.32, 127.08, 126.74, 126.41, 126.16, 125.93, 124.46, 64.72, 62.59, 35.13, 29.76.

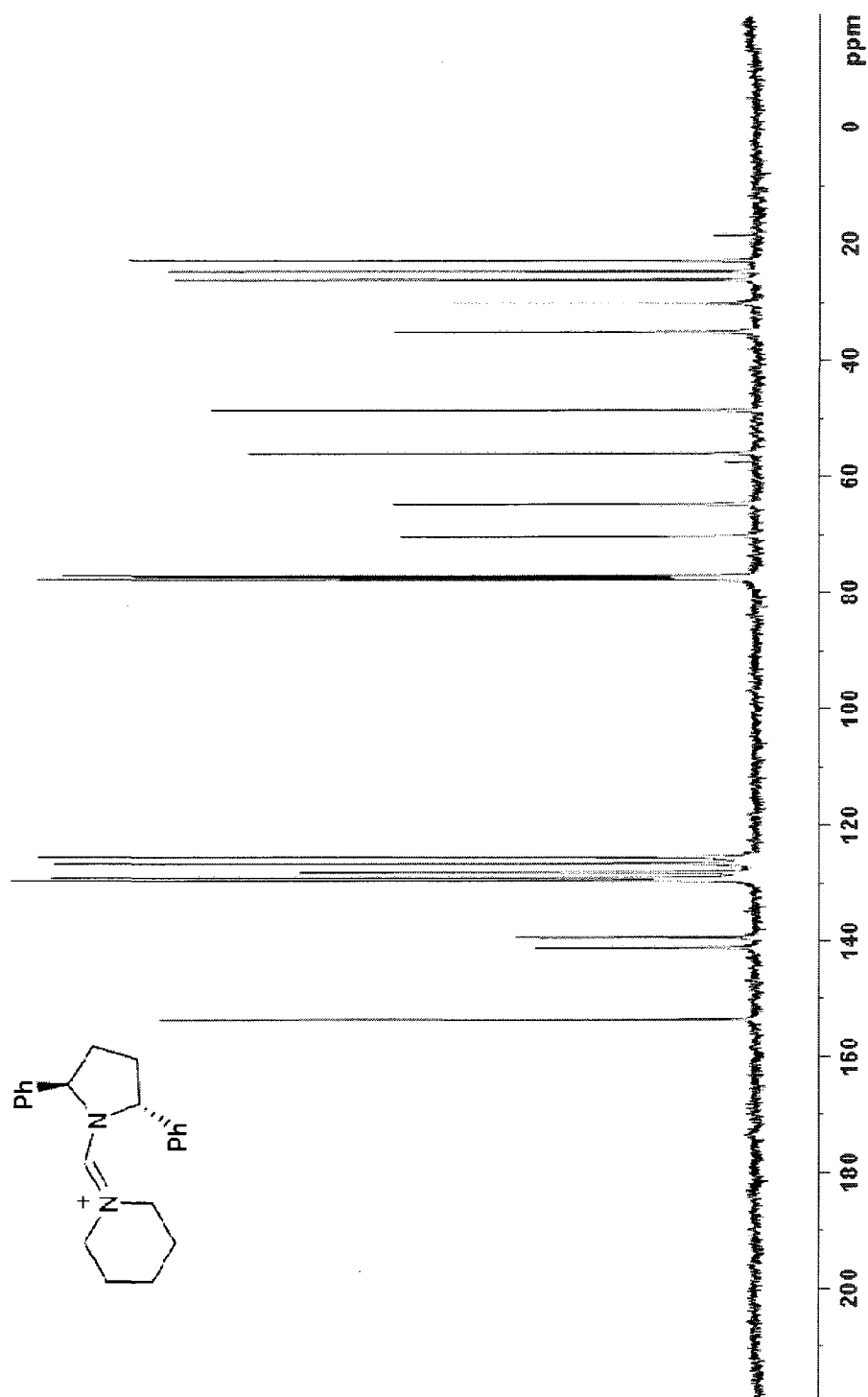


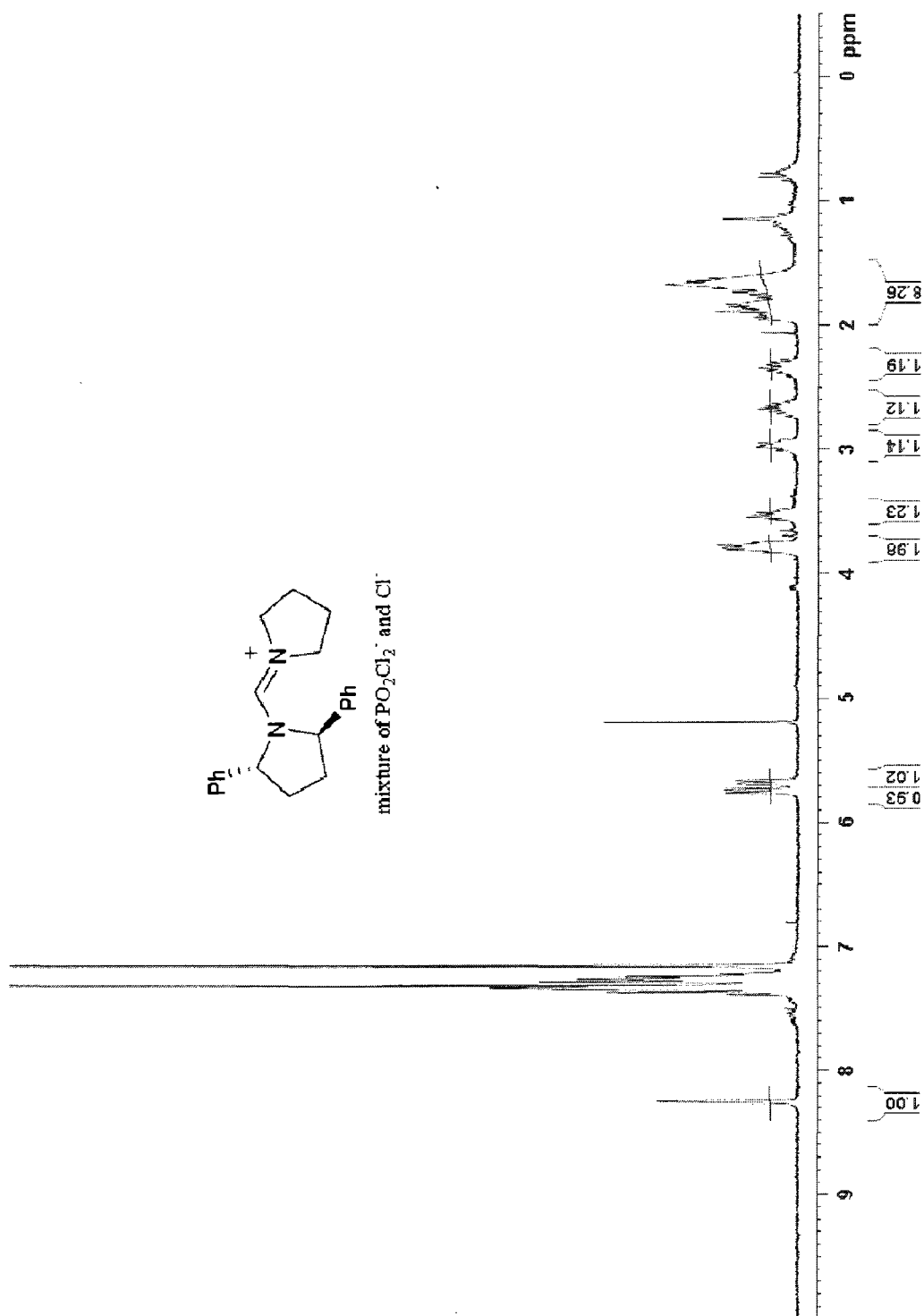


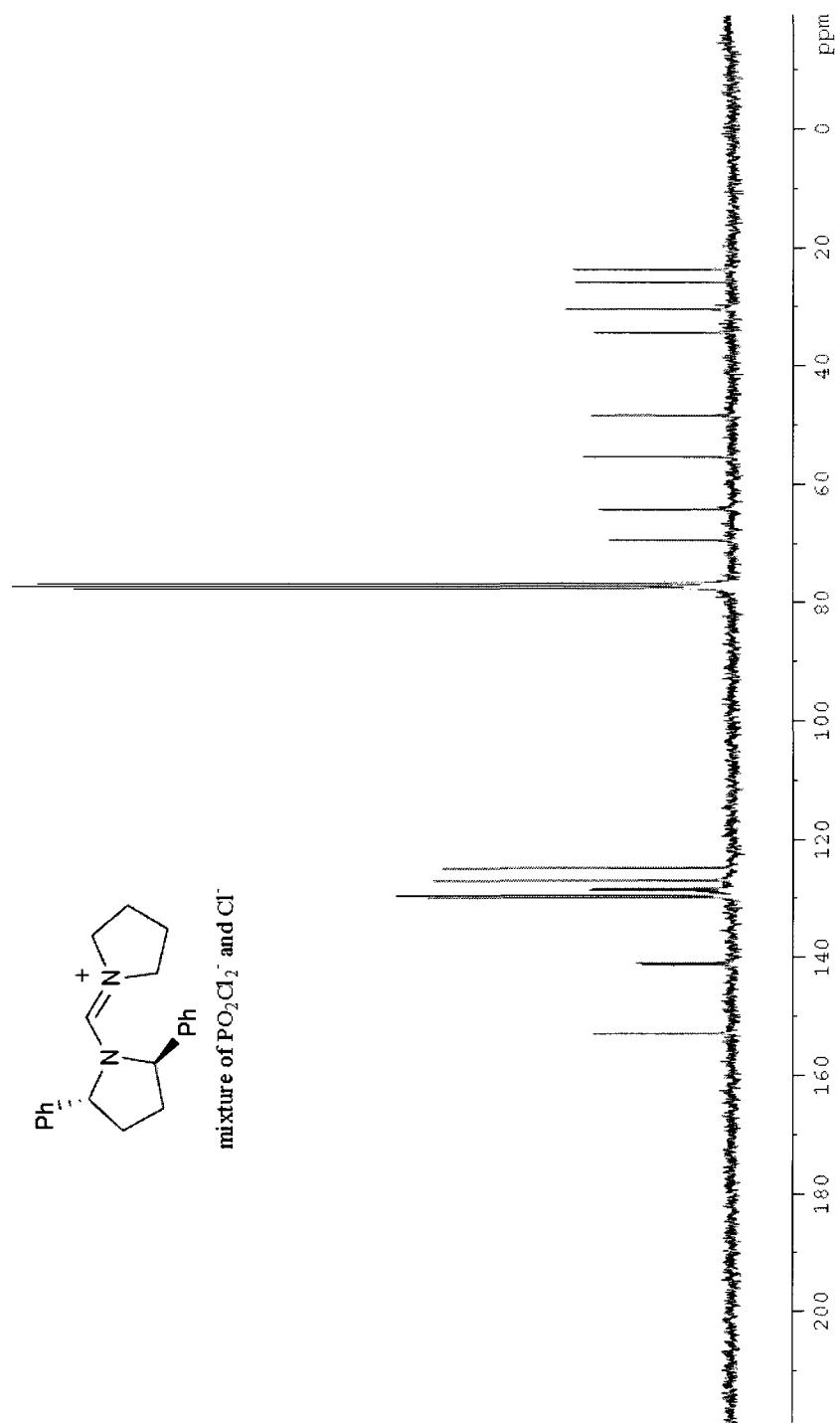












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Appendix I: Crystal structure tables for 19a

The crystal structure solved by Dr. Jorge Tiburcio

Ortep 3, thermal ellipsoids shown at 30%

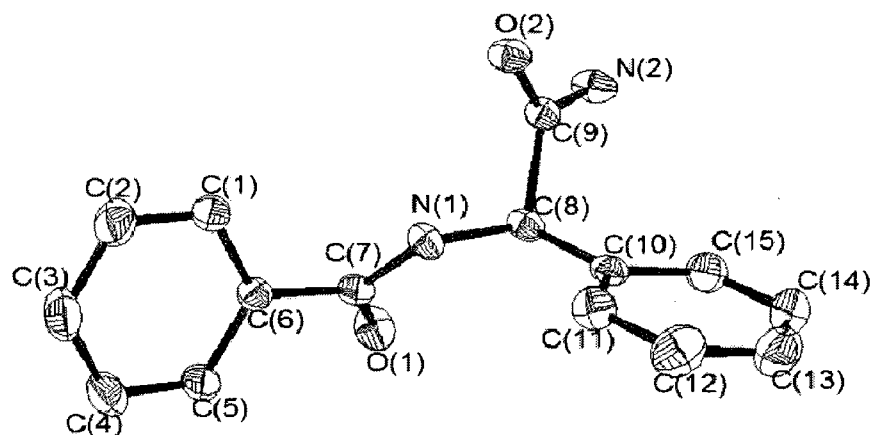


Table 1. Crystal data and structure refinement for **2**.

Identification code	jtk77	
Empirical formula	C ₁₅ H ₁₄ N ₂ O ₂	
Formula weight	254.28	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 18.101(4) Å	a = 90°.
	b = 7.1667(14) Å	b = 101.16(3)°.
	c = 20.677(4) Å	g = 90°.
Volume	2631.6(9) Å ³	
Z	8	
Density (calculated)	1.284 Mg/m ³	
Absorption coefficient	0.087 mm ⁻¹	
F(000)	1072	
Crystal size	0.25 x 0.25 x 0.02 mm ³	

Theta range for data collection	2.037 to 24.99°
Index ranges	-16<=h<=21, -8<=k<=7, -24<=l<=24
Reflections collected	7631
Independent reflections	2245 [R(int) = 0.0527]
Completeness to theta = 24.99°	96.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9984 and 0.9786
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2245 / 0 / 172
Goodness-of-fit on F ²	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0446, wR2 = 0.1018
R indices (all data)	R1 = 0.0692, wR2 = 0.1161
Largest diff. peak and hole	0.136 and -0.162 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 2. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	2293(1)	-105(2)	4491(1)	57(1)
N(1)	1220(1)	-109(2)	4898(1)	39(1)
C(1)	564(1)	-2335(3)	3753(1)	52(1)
O(2)	139(1)	2467(2)	4994(1)	45(1)
N(2)	1033(1)	4680(2)	5234(1)	49(1)
C(2)	272(1)	-3865(3)	3393(1)	71(1)
C(3)	723(1)	-5339(3)	3315(1)	74(1)
C(4)	1477(1)	-5279(3)	3581(1)	66(1)
C(5)	1779(1)	-3745(3)	3934(1)	50(1)
C(6)	1325(1)	-2266(2)	4040(1)	38(1)
C(7)	1658(1)	-721(2)	4485(1)	38(1)
C(8)	1410(1)	1437(2)	5348(1)	38(1)
C(9)	805(1)	2937(2)	5167(1)	36(1)
C(10)	1454(1)	910(2)	6071(1)	40(1)
C(11)	1198(1)	-782(3)	6260(1)	54(1)
C(12)	1240(1)	-1185(4)	6921(1)	74(1)
C(13)	1524(1)	74(4)	7395(1)	77(1)
C(14)	1778(1)	1765(4)	7220(1)	72(1)
C(15)	1744(1)	2187(3)	6561(1)	56(1)

Table 3. Bond lengths [Å] and angles [°] for 2.

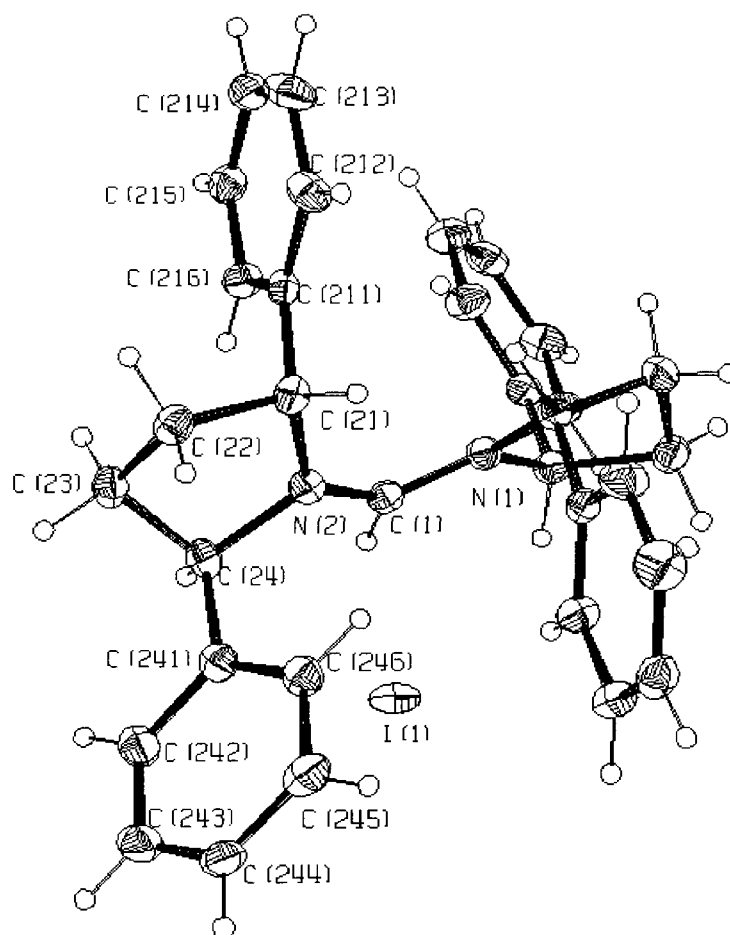
O(1)-C(7)	1.2292(18)
N(1)-C(7)	1.345(2)
N(1)-C(8)	1.445(2)
C(1)-C(2)	1.373(3)
C(1)-C(6)	1.390(2)
O(2)-C(9)	1.2351(17)
N(2)-C(9)	1.315(2)
C(2)-C(3)	1.364(3)
C(3)-C(4)	1.369(3)
C(4)-C(5)	1.374(3)
C(5)-C(6)	1.384(2)
C(6)-C(7)	1.491(2)
C(8)-C(10)	1.527(2)
C(8)-C(9)	1.529(2)
C(10)-C(11)	1.382(3)
C(10)-C(15)	1.392(2)
C(11)-C(12)	1.384(3)
C(12)-C(13)	1.359(3)
C(13)-C(14)	1.369(3)
C(14)-C(15)	1.385(3)
C(7)-N(1)-C(8)	124.27(13)
C(2)-C(1)-C(6)	120.42(17)
C(3)-C(2)-C(1)	120.35(18)
C(2)-C(3)-C(4)	120.1(2)
C(3)-C(4)-C(5)	120.08(19)
C(4)-C(5)-C(6)	120.64(16)
C(5)-C(6)-C(1)	118.31(16)
C(5)-C(6)-C(7)	118.99(14)
C(1)-C(6)-C(7)	122.61(14)
O(1)-C(7)-N(1)	122.76(16)
O(1)-C(7)-C(6)	122.58(14)
N(1)-C(7)-C(6)	114.62(13)
N(1)-C(8)-C(10)	113.66(13)
N(1)-C(8)-C(9)	108.17(13)

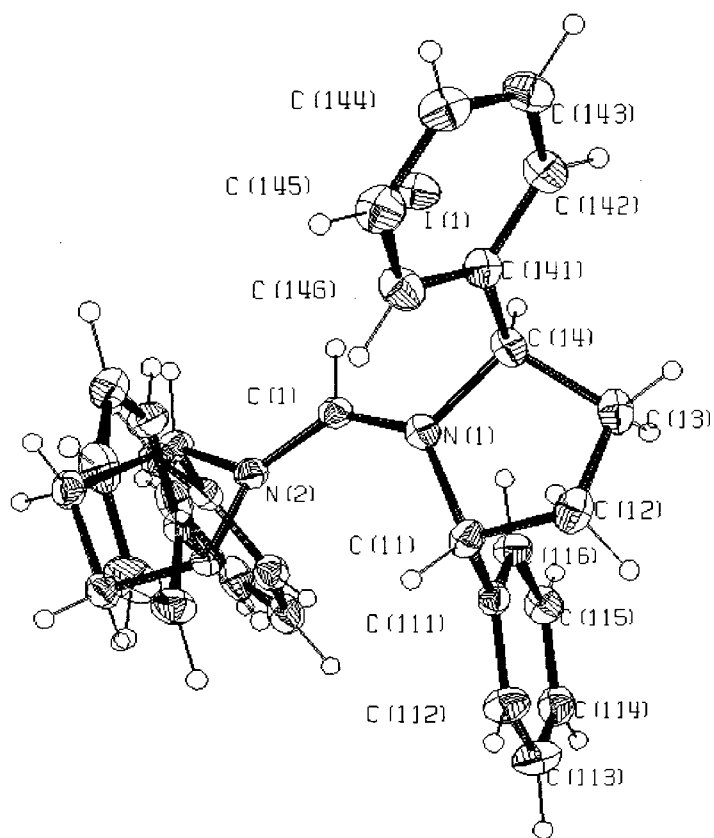
C(10)-C(8)-C(9)	108.21(12)
O(2)-C(9)-N(2)	123.96(14)
O(2)-C(9)-C(8)	119.45(14)
N(2)-C(9)-C(8)	116.54(13)
C(11)-C(10)-C(15)	118.09(18)
C(11)-C(10)-C(8)	122.48(16)
C(15)-C(10)-C(8)	119.41(16)
C(10)-C(11)-C(12)	120.3(2)
C(13)-C(12)-C(11)	121.0(2)
C(12)-C(13)-C(14)	119.7(2)
C(13)-C(14)-C(15)	120.1(2)
C(14)-C(15)-C(10)	120.8(2)

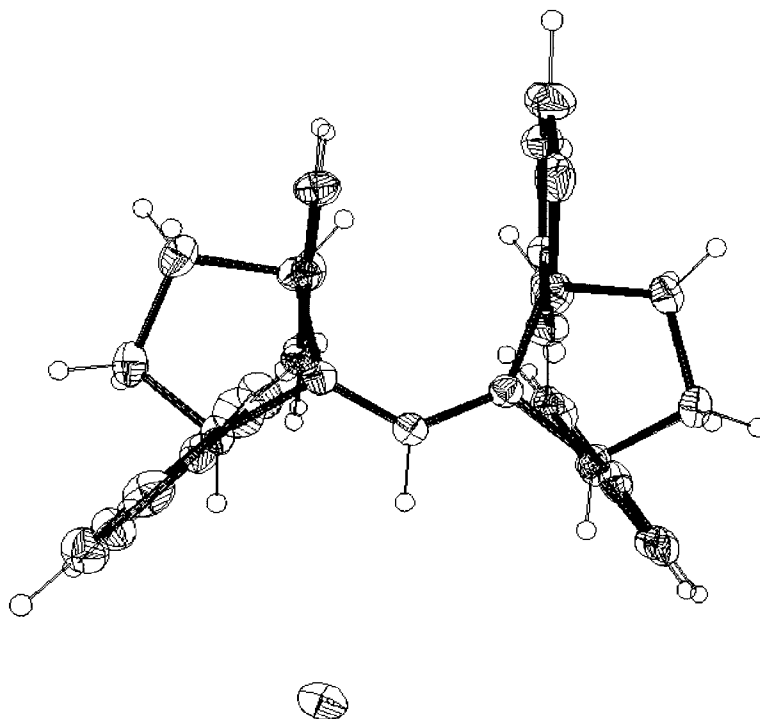
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 2. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	36(1)	66(1)	72(1)	-14(1)	23(1)	-10(1)
N(1)	31(1)	36(1)	52(1)	-8(1)	15(1)	-4(1)
C(1)	37(1)	67(1)	52(1)	-11(1)	6(1)	13(1)
O(2)	30(1)	37(1)	66(1)	0(1)	6(1)	-2(1)
N(2)	33(1)	31(1)	81(1)	2(1)	6(1)	-2(1)
C(2)	39(1)	97(2)	73(2)	-34(1)	2(1)	1(1)
C(3)	60(1)	84(2)	78(2)	-42(1)	10(1)	-6(1)
C(4)	57(1)	66(2)	76(2)	-25(1)	14(1)	12(1)
C(5)	37(1)	58(1)	54(1)	-9(1)	9(1)	8(1)
C(6)	33(1)	45(1)	38(1)	-1(1)	11(1)	5(1)
C(7)	30(1)	40(1)	44(1)	3(1)	10(1)	4(1)
C(8)	26(1)	34(1)	53(1)	-4(1)	10(1)	-1(1)
C(9)	31(1)	36(1)	43(1)	0(1)	11(1)	-1(1)
C(10)	28(1)	40(1)	51(1)	-2(1)	6(1)	7(1)
C(11)	54(1)	51(1)	57(1)	1(1)	10(1)	-2(1)
C(12)	78(1)	77(2)	66(2)	18(1)	14(1)	-3(1)
C(13)	80(2)	99(2)	50(2)	9(1)	11(1)	13(1)
C(14)	76(1)	84(2)	52(1)	-15(1)	-3(1)	13(1)
C(15)	52(1)	52(1)	60(1)	-7(1)	2(1)	4(1)

Appendix II: Crystal structure tables for 102



**Table 1.** Crystal data and structure refinement for p32_2.

Identification code	p32_2	
Empirical formula	C33 H33 I N2	
Formula weight	584.51	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	P3(2)	
Unit cell dimensions	a = 10.0551(7) Å	a = 90°.
	b = 10.0551(7) Å	b = 90°.
	c = 23.239(2) Å	g = 120°.
Volume	2034.8(3) Å ³	
Z	3	
Density (calculated)	1.431 Mg/m ³	
Absorption coefficient	1.204 mm ⁻¹	
F(000)	894	

Crystal size	0.40 x 0.30 x 0.30 mm ³
Theta range for data collection	2.50 to 27.50°.
Index ranges	-12<=h<=13, -12<=k<=13, -29<=l<=30
Reflections collected	22606
Independent reflections	6073 [R(int) = 0.0246]
Completeness to theta = 27.50°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.697 and 0.619
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6073 / 1 / 325
Goodness-of-fit on F ²	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0262, wR2 = 0.0614
R indices (all data)	R1 = 0.0288, wR2 = 0.0624
Absolute structure parameter	-0.015(11)
Largest diff. peak and hole	0.908 and -0.378 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for p32_2. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(213)	8645(4)	2407(4)	9677(2)	53(1)
C(1)	5707(3)	-2717(3)	10912(1)	29(1)
C(11)	8551(3)	-1591(3)	11015(1)	34(1)
C(12)	9540(3)	-2166(4)	10727(1)	43(1)
C(13)	8491(3)	-3899(3)	10726(1)	42(1)
C(14)	6946(3)	-4089(3)	10537(1)	36(1)
C(21)	6608(3)	113(3)	11006(1)	33(1)
C(22)	5675(3)	827(3)	11257(1)	37(1)
C(23)	4019(3)	-387(3)	11140(1)	39(1)
C(24)	4003(3)	-1865(3)	11305(1)	35(1)
C(111)	8585(3)	-1680(3)	11666(1)	31(1)
C(112)	9778(3)	-482(3)	11956(1)	46(1)
C(113)	9911(4)	-555(4)	12547(1)	54(1)
C(114)	8879(4)	-1843(4)	12848(1)	44(1)
C(115)	7683(3)	-3028(3)	12569(1)	42(1)
C(116)	7525(3)	-2961(3)	11974(1)	38(1)
C(141)	6766(3)	-4172(3)	9887(1)	36(1)
C(142)	6386(3)	-5552(3)	9620(1)	43(1)
C(143)	6267(4)	-5673(4)	9026(1)	49(1)
C(144)	6499(3)	-4437(4)	8696(1)	46(1)
C(145)	6881(4)	-3065(4)	8955(1)	51(1)
C(146)	7023(4)	-2932(4)	9550(1)	45(1)
C(211)	6998(2)	546(2)	10382(1)	30(1)
C(212)	8334(3)	1885(3)	10247(1)	41(1)
C(214)	7636(4)	1564(4)	9245(1)	45(1)
C(215)	6334(3)	222(3)	9371(1)	40(1)
C(216)	6003(3)	-280(3)	9936(1)	36(1)
C(241)	3822(3)	-2128(3)	11951(1)	36(1)
C(242)	2360(3)	-2723(3)	12184(1)	43(1)
C(243)	2127(4)	-2875(3)	12772(1)	50(1)
C(244)	3372(4)	-2413(4)	13135(1)	46(1)

C(245)	4824(4)	-1844(4)	12913(1)	48(1)
C(246)	5052(3)	-1695(3)	12319(1)	40(1)
N(1)	6996(2)	-2690(2)	10787(1)	32(1)
N(2)	5534(2)	-1564(2)	11091(1)	31(1)
I(1)	2745(1)	-6931(1)	11004(1)	47(1)

Table 3. Bond lengths [Å] and angles [°] for p32_2.

C(213)-C(214)	1.377(5)
C(213)-C(212)	1.401(4)
C(213)-H(213)	0.9500
C(1)-N(1)	1.315(3)
C(1)-N(2)	1.322(3)
C(1)-H(1)	0.9500
C(11)-N(1)	1.489(4)
C(11)-C(111)	1.517(4)
C(11)-C(12)	1.531(4)
C(11)-H(11)	1.0000
C(12)-C(13)	1.520(4)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.530(4)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-N(1)	1.499(3)
C(14)-C(141)	1.520(4)
C(14)-H(14)	1.0000
C(21)-N(2)	1.493(3)
C(21)-C(211)	1.509(4)
C(21)-C(22)	1.551(3)
C(21)-H(21)	1.0000
C(22)-C(23)	1.517(4)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-C(24)	1.527(4)
C(23)-H(23A)	0.9900
C(23)-H(23B)	0.9900
C(24)-N(2)	1.497(3)
C(24)-C(241)	1.520(4)
C(24)-H(24)	1.0000
C(111)-C(112)	1.378(4)
C(111)-C(116)	1.391(4)

C(112)-C(113)	1.385(4)
C(112)-H(112)	0.9500
C(113)-C(114)	1.378(5)
C(113)-H(113)	0.9500
C(114)-C(115)	1.361(4)
C(114)-H(114)	0.9500
C(115)-C(116)	1.398(4)
C(115)-H(115)	0.9500
C(116)-H(116)	0.9500
C(141)-C(146)	1.383(4)
C(141)-C(142)	1.388(4)
C(142)-C(143)	1.384(4)
C(142)-H(142)	0.9500
C(143)-C(144)	1.378(5)
C(143)-H(143)	0.9500
C(144)-C(145)	1.374(5)
C(144)-H(144)	0.9500
C(145)-C(146)	1.388(4)
C(145)-H(145)	0.9500
C(146)-H(146)	0.9500
C(211)-C(212)	1.381(3)
C(211)-C(216)	1.390(4)
C(212)-H(212)	0.9500
C(214)-C(215)	1.361(5)
C(214)-H(214)	0.9500
C(215)-C(216)	1.387(4)
C(215)-H(215)	0.9500
C(216)-H(216)	0.9500
C(241)-C(246)	1.383(4)
C(241)-C(242)	1.390(4)
C(242)-C(243)	1.381(4)
C(242)-H(242)	0.9500
C(243)-C(244)	1.384(5)
C(243)-H(243)	0.9500
C(244)-C(245)	1.375(5)
C(244)-H(244)	0.9500

C(245)-C(246)	1.394(4)
C(245)-H(245)	0.9500
C(246)-H(246)	0.9500
C(214)-C(213)-C(212)	120.0(3)
C(214)-C(213)-H(213)	120.0
C(212)-C(213)-H(213)	120.0
N(1)-C(1)-N(2)	127.7(2)
N(1)-C(1)-H(1)	116.1
N(2)-C(1)-H(1)	116.1
N(1)-C(11)-C(111)	110.9(2)
N(1)-C(11)-C(12)	101.8(2)
C(111)-C(11)-C(12)	112.1(2)
N(1)-C(11)-H(11)	110.6
C(111)-C(11)-H(11)	110.6
C(12)-C(11)-H(11)	110.6
C(13)-C(12)-C(11)	103.0(2)
C(13)-C(12)-H(12A)	111.2
C(11)-C(12)-H(12A)	111.2
C(13)-C(12)-H(12B)	111.2
C(11)-C(12)-H(12B)	111.2
H(12A)-C(12)-H(12B)	109.1
C(12)-C(13)-C(14)	102.9(2)
C(12)-C(13)-H(13A)	111.2
C(14)-C(13)-H(13A)	111.2
C(12)-C(13)-H(13B)	111.2
C(14)-C(13)-H(13B)	111.2
H(13A)-C(13)-H(13B)	109.1
N(1)-C(14)-C(141)	112.6(2)
N(1)-C(14)-C(13)	102.5(2)
C(141)-C(14)-C(13)	112.1(2)
N(1)-C(14)-H(14)	109.8
C(141)-C(14)-H(14)	109.8
C(13)-C(14)-H(14)	109.8
N(2)-C(21)-C(211)	112.9(2)
N(2)-C(21)-C(22)	102.1(2)
C(211)-C(21)-C(22)	111.0(2)

N(2)-C(21)-H(21)	110.2
C(211)-C(21)-H(21)	110.2
C(22)-C(21)-H(21)	110.2
C(23)-C(22)-C(21)	103.6(2)
C(23)-C(22)-H(22A)	111.0
C(21)-C(22)-H(22A)	111.0
C(23)-C(22)-H(22B)	111.0
C(21)-C(22)-H(22B)	111.0
H(22A)-C(22)-H(22B)	109.0
C(22)-C(23)-C(24)	102.2(2)
C(22)-C(23)-H(23A)	111.3
C(24)-C(23)-H(23A)	111.3
C(22)-C(23)-H(23B)	111.3
C(24)-C(23)-H(23B)	111.3
H(23A)-C(23)-H(23B)	109.2
N(2)-C(24)-C(241)	112.6(2)
N(2)-C(24)-C(23)	102.2(2)
C(241)-C(24)-C(23)	111.0(2)
N(2)-C(24)-H(24)	110.3
C(241)-C(24)-H(24)	110.3
C(23)-C(24)-H(24)	110.3
C(112)-C(111)-C(116)	119.1(2)
C(112)-C(111)-C(11)	118.2(2)
C(116)-C(111)-C(11)	122.6(2)
C(111)-C(112)-C(113)	120.3(3)
C(111)-C(112)-H(112)	119.9
C(113)-C(112)-H(112)	119.9
C(114)-C(113)-C(112)	120.4(3)
C(114)-C(113)-H(113)	119.8
C(112)-C(113)-H(113)	119.8
C(115)-C(114)-C(113)	120.1(3)
C(115)-C(114)-H(114)	119.9
C(113)-C(114)-H(114)	119.9
C(114)-C(115)-C(116)	120.0(3)
C(114)-C(115)-H(115)	120.0
C(116)-C(115)-H(115)	120.0

C(111)-C(116)-C(115)	120.1(2)
C(111)-C(116)-H(116)	120.0
C(115)-C(116)-H(116)	120.0
C(146)-C(141)-C(142)	118.8(3)
C(146)-C(141)-C(14)	123.4(2)
C(142)-C(141)-C(14)	117.7(2)
C(143)-C(142)-C(141)	120.1(3)
C(143)-C(142)-H(142)	119.9
C(141)-C(142)-H(142)	119.9
C(144)-C(143)-C(142)	120.5(3)
C(144)-C(143)-H(143)	119.8
C(142)-C(143)-H(143)	119.8
C(145)-C(144)-C(143)	119.9(3)
C(145)-C(144)-H(144)	120.1
C(143)-C(144)-H(144)	120.1
C(144)-C(145)-C(146)	119.8(3)
C(144)-C(145)-H(145)	120.1
C(146)-C(145)-H(145)	120.1
C(141)-C(146)-C(145)	120.9(3)
C(141)-C(146)-H(146)	119.6
C(145)-C(146)-H(146)	119.6
C(212)-C(211)-C(216)	118.1(3)
C(212)-C(211)-C(21)	119.1(2)
C(216)-C(211)-C(21)	122.6(2)
C(211)-C(212)-C(213)	120.5(3)
C(211)-C(212)-H(212)	119.8
C(213)-C(212)-H(212)	119.8
C(215)-C(214)-C(213)	120.0(3)
C(215)-C(214)-H(214)	120.0
C(213)-C(214)-H(214)	120.0
C(214)-C(215)-C(216)	120.1(3)
C(214)-C(215)-H(215)	120.0
C(216)-C(215)-H(215)	120.0
C(215)-C(216)-C(211)	121.2(2)
C(215)-C(216)-H(216)	119.4
C(211)-C(216)-H(216)	119.4

C(246)-C(241)-C(242)	118.8(2)
C(246)-C(241)-C(24)	123.1(2)
C(242)-C(241)-C(24)	117.9(2)
C(243)-C(242)-C(241)	121.1(3)
C(243)-C(242)-H(242)	119.4
C(241)-C(242)-H(242)	119.4
C(242)-C(243)-C(244)	119.5(3)
C(242)-C(243)-H(243)	120.3
C(244)-C(243)-H(243)	120.3
C(245)-C(244)-C(243)	120.3(3)
C(245)-C(244)-H(244)	119.9
C(243)-C(244)-H(244)	119.9
C(244)-C(245)-C(246)	120.0(3)
C(244)-C(245)-H(245)	120.0
C(246)-C(245)-H(245)	120.0
C(241)-C(246)-C(245)	120.3(3)
C(241)-C(246)-H(246)	119.8
C(245)-C(246)-H(246)	119.8
C(1)-N(1)-C(11)	126.5(2)
C(1)-N(1)-C(14)	119.7(2)
C(11)-N(1)-C(14)	111.3(2)
C(1)-N(2)-C(21)	127.7(2)
C(1)-N(2)-C(24)	120.0(2)
C(21)-N(2)-C(24)	111.21(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for p32_2. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(213)	46(2)	37(2)	63(2)	3(1)	23(2)	10(1)
C(1)	32(1)	31(1)	24(1)	-1(1)	-3(1)	15(1)
C(11)	30(1)	35(1)	37(1)	10(1)	2(1)	16(1)
C(12)	39(2)	59(2)	37(2)	8(1)	7(1)	29(1)
C(13)	53(2)	52(2)	36(1)	6(1)	6(1)	37(2)
C(14)	44(1)	35(1)	34(1)	3(1)	6(1)	24(1)
C(21)	33(1)	29(1)	37(1)	-5(1)	-8(1)	16(1)
C(22)	46(1)	35(1)	35(1)	-4(1)	-2(1)	24(1)
C(23)	43(1)	48(2)	37(1)	-3(1)	-2(1)	31(1)
C(24)	28(1)	40(1)	38(1)	-7(1)	-3(1)	17(1)
C(111)	31(1)	31(1)	35(1)	3(1)	-1(1)	17(1)
C(112)	37(1)	42(2)	47(2)	2(1)	-1(1)	10(1)
C(113)	46(2)	56(2)	49(2)	-12(2)	-13(1)	17(2)
C(114)	53(2)	54(2)	35(2)	-2(1)	-5(1)	34(2)
C(115)	49(2)	40(1)	36(1)	6(1)	2(1)	23(1)
C(116)	39(1)	34(1)	36(1)	1(1)	-4(1)	14(1)
C(141)	36(1)	40(1)	33(1)	3(1)	6(1)	20(1)
C(142)	50(2)	38(1)	41(2)	5(1)	7(1)	21(1)
C(143)	54(2)	46(2)	41(2)	-9(1)	5(1)	21(1)
C(144)	41(2)	60(2)	32(1)	0(1)	8(1)	21(1)
C(145)	58(2)	55(2)	38(2)	7(1)	4(1)	28(2)
C(146)	60(2)	42(2)	37(2)	2(1)	6(1)	27(1)
C(211)	28(1)	28(1)	37(1)	-3(1)	-3(1)	16(1)
C(212)	33(1)	36(1)	49(2)	-8(1)	3(1)	12(1)
C(214)	56(2)	49(2)	42(2)	9(1)	15(1)	34(2)
C(215)	40(1)	47(2)	39(2)	2(1)	-4(1)	24(1)
C(216)	34(1)	35(1)	35(1)	2(1)	-5(1)	13(1)
C(241)	39(1)	30(1)	40(1)	-3(1)	1(1)	19(1)
C(242)	38(1)	35(1)	53(2)	0(1)	3(1)	17(1)
C(243)	56(2)	41(2)	57(2)	14(1)	21(2)	28(1)
C(244)	66(2)	47(2)	38(2)	14(1)	14(1)	37(2)

C(245)	64(2)	48(2)	38(2)	2(1)	-3(1)	34(2)
C(246)	44(2)	42(1)	37(1)	-3(1)	1(1)	25(1)
N(1)	35(1)	33(1)	30(1)	2(1)	2(1)	17(1)
N(2)	30(1)	32(1)	29(1)	-3(1)	-2(1)	15(1)
I(1)	57(1)	39(1)	31(1)	5(1)	7(1)	13(1)

Appendix III: Crystal structure tables for **117**

It exhibits a perfect C_2 -symmetry with a half of the molecule in the asymmetric unit.

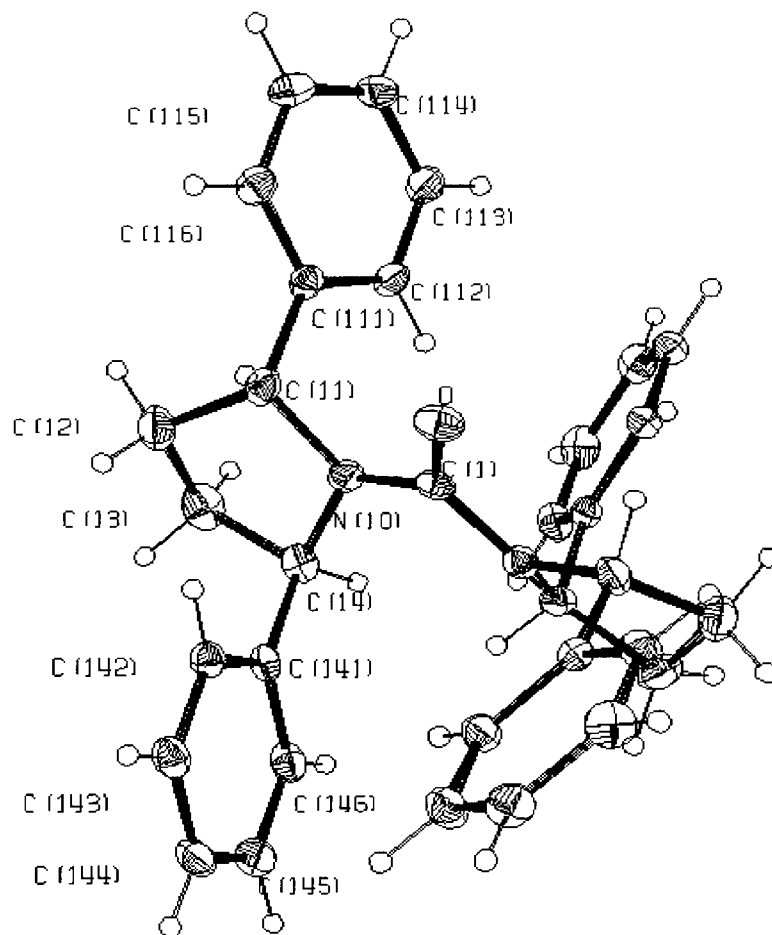


Table 1. Crystal data and structure refinement for c2.

Identification code	c2
Empirical formula	C ₃₃ H ₃₂ N ₂ O
Formula weight	472.61

Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 17.5058(17) Å	a = 90°.
	b = 6.6127(6) Å	b = 112.9900(10)°.
	c = 11.9058(11) Å	g = 90°.
Volume	1268.8(2) Å ³	
Z	2	
Density (calculated)	1.237 Mg/m ³	
Absorption coefficient	0.074 mm ⁻¹	
F(000)	504	
Crystal size	0.60 x 0.40 x 0.40 mm ³	
Theta range for data collection	1.86 to 27.50°.	
Index ranges	-22<=h<=22, -8<=k<=8, -14<=l<=15	
Reflections collected	7121	
Independent reflections	1557 [R(int) = 0.0215]	
Completeness to theta = 27.50°	98.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.971 and 0.863	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	1557 / 1 / 164	
Goodness-of-fit on F ²	1.175	
Final R indices [I>2sigma(I)]	R1 = 0.0464, wR2 = 0.1289	
R indices (all data)	R1 = 0.0507, wR2 = 0.1407	
Absolute structure parameter	-10(10)	
Largest diff. peak and hole	0.377 and -0.243 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for c2. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O	0	11175(4)	10000	40(1)
C(1)	0	9311(5)	10000	27(1)
N(10)	706(1)	8258(4)	10674(2)	30(1)
C(11)	1428(2)	9479(5)	11459(2)	37(1)
C(12)	2167(2)	8166(6)	11572(3)	50(1)
C(13)	1819(2)	6031(6)	11372(3)	50(1)
C(14)	943(2)	6237(4)	10377(2)	33(1)
C(111)	1396(1)	10018(4)	12681(2)	30(1)
C(112)	919(1)	8961(4)	13182(2)	34(1)
C(113)	920(2)	9525(5)	14304(2)	40(1)
C(114)	1393(2)	11148(5)	14938(2)	41(1)
C(115)	1876(2)	12190(5)	14453(3)	43(1)
C(116)	1875(2)	11620(4)	13331(2)	37(1)
C(141)	902(1)	6093(4)	9080(2)	29(1)
C(142)	1160(1)	7663(4)	8536(2)	31(1)
C(143)	1140(2)	7457(5)	7360(2)	37(1)
C(144)	847(2)	5686(5)	6715(2)	42(1)
C(145)	571(2)	4144(5)	7233(3)	44(1)
C(146)	604(2)	4322(4)	8417(3)	38(1)

Table 3. Bond lengths [Å] and angles [°] for c2.

O-C(1)	1.233(5)
C(1)-N(10)#1	1.372(3)
C(1)-N(10)	1.372(3)
N(10)-C(14)	1.482(4)
N(10)-C(11)	1.483(3)
C(11)-C(111)	1.520(3)
C(11)-C(12)	1.520(4)
C(11)-H(11)	1.0000
C(12)-C(13)	1.519(6)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.534(4)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(141)	1.520(3)
C(14)-H(14)	1.0000
C(111)-C(116)	1.385(4)
C(111)-C(112)	1.389(3)
C(112)-C(113)	1.387(3)
C(112)-H(112)	0.9500
C(113)-C(114)	1.385(4)
C(113)-H(113)	0.9500
C(114)-C(115)	1.379(4)
C(114)-H(114)	0.9500
C(115)-C(116)	1.387(4)
C(115)-H(115)	0.9500
C(116)-H(116)	0.9500
C(141)-C(142)	1.390(3)
C(141)-C(146)	1.395(4)
C(142)-C(143)	1.393(3)
C(142)-H(142)	0.9500
C(143)-C(144)	1.385(4)
C(143)-H(143)	0.9500
C(144)-C(145)	1.373(4)

C(144)-H(144)	0.9500
C(145)-C(146)	1.393(4)
C(145)-H(145)	0.9500
C(146)-H(146)	0.9500
O-C(1)-N(10)#1	120.50(16)
O-C(1)-N(10)	120.50(16)
N(10)#1-C(1)-N(10)	119.0(3)
C(1)-N(10)-C(14)	126.2(2)
C(1)-N(10)-C(11)	116.4(2)
C(14)-N(10)-C(11)	113.1(2)
N(10)-C(11)-C(111)	112.98(18)
N(10)-C(11)-C(12)	103.4(2)
C(111)-C(11)-C(12)	113.4(2)
N(10)-C(11)-H(11)	109.0
C(111)-C(11)-H(11)	109.0
C(12)-C(11)-H(11)	109.0
C(13)-C(12)-C(11)	104.0(2)
C(13)-C(12)-H(12A)	111.0
C(11)-C(12)-H(12A)	111.0
C(13)-C(12)-H(12B)	111.0
C(11)-C(12)-H(12B)	111.0
H(12A)-C(12)-H(12B)	109.0
C(12)-C(13)-C(14)	104.9(2)
C(12)-C(13)-H(13A)	110.8
C(14)-C(13)-H(13A)	110.8
C(12)-C(13)-H(13B)	110.8
C(14)-C(13)-H(13B)	110.8
H(13A)-C(13)-H(13B)	108.8
N(10)-C(14)-C(141)	113.06(19)
N(10)-C(14)-C(13)	100.6(2)
C(141)-C(14)-C(13)	114.6(2)
N(10)-C(14)-H(14)	109.4
C(141)-C(14)-H(14)	109.4
C(13)-C(14)-H(14)	109.4
C(116)-C(111)-C(112)	118.6(2)
C(116)-C(111)-C(11)	118.3(2)

C(112)-C(111)-C(11)	123.1(2)
C(113)-C(112)-C(111)	120.2(2)
C(113)-C(112)-H(112)	119.9
C(111)-C(112)-H(112)	119.9
C(114)-C(113)-C(112)	120.5(2)
C(114)-C(113)-H(113)	119.7
C(112)-C(113)-H(113)	119.7
C(115)-C(114)-C(113)	119.6(2)
C(115)-C(114)-H(114)	120.2
C(113)-C(114)-H(114)	120.2
C(114)-C(115)-C(116)	119.7(3)
C(114)-C(115)-H(115)	120.1
C(116)-C(115)-H(115)	120.1
C(111)-C(116)-C(115)	121.3(2)
C(111)-C(116)-H(116)	119.4
C(115)-C(116)-H(116)	119.4
C(142)-C(141)-C(146)	118.8(2)
C(142)-C(141)-C(14)	122.1(2)
C(146)-C(141)-C(14)	119.1(2)
C(141)-C(142)-C(143)	120.7(2)
C(141)-C(142)-H(142)	119.6
C(143)-C(142)-H(142)	119.6
C(144)-C(143)-C(142)	119.9(3)
C(144)-C(143)-H(143)	120.1
C(142)-C(143)-H(143)	120.1
C(145)-C(144)-C(143)	119.9(2)
C(145)-C(144)-H(144)	120.1
C(143)-C(144)-H(144)	120.1
C(144)-C(145)-C(146)	120.6(3)
C(144)-C(145)-H(145)	119.7
C(146)-C(145)-H(145)	119.7
C(145)-C(146)-C(141)	120.2(2)
C(145)-C(146)-H(146)	119.9
C(141)-C(146)-H(146)	119.9

Symmetry transformations used to generate equivalent atoms: #1 -x,y,-z+2

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for c2. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O	55(2)	31(1)	36(1)	0	21(1)	0
C(1)	37(2)	30(2)	18(1)	0	15(1)	0
N(10)	30(1)	35(1)	24(1)	-1(1)	12(1)	-4(1)
C(11)	31(1)	52(2)	28(1)	-1(1)	13(1)	-11(1)
C(12)	33(1)	77(2)	41(1)	0(2)	14(1)	3(2)
C(13)	45(2)	61(2)	42(1)	17(2)	14(1)	19(2)
C(14)	35(1)	32(1)	33(1)	9(1)	16(1)	6(1)
C(111)	25(1)	35(1)	25(1)	3(1)	7(1)	0(1)
C(112)	31(1)	43(2)	26(1)	-2(1)	9(1)	-10(1)
C(113)	37(1)	55(2)	31(1)	-2(1)	15(1)	-9(1)
C(114)	44(1)	47(2)	31(1)	-8(1)	13(1)	1(1)
C(115)	49(2)	34(1)	43(2)	-10(1)	14(1)	-8(1)
C(116)	39(1)	35(1)	39(1)	2(1)	16(1)	-6(1)
C(141)	25(1)	30(1)	34(1)	4(1)	14(1)	5(1)
C(142)	31(1)	32(1)	30(1)	2(1)	13(1)	0(1)
C(143)	36(1)	44(2)	34(1)	6(1)	18(1)	4(1)
C(144)	40(1)	55(2)	34(1)	-6(1)	20(1)	7(1)
C(145)	42(1)	39(2)	53(2)	-13(1)	21(1)	0(1)
C(146)	37(1)	30(1)	54(2)	0(1)	25(1)	0(1)

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